Sc.

FEBRUARY 1959
VOL. XIX NO. 2

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

RP
101
F55

Published by Grune & Stratton, Inc.

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

new

"flavor-timed"

dual-action

coronary vasodilator

Dilcoron

TRADEMARK

ORAL

for **Sustained** *coronary vasodilation and protection against anginal attack*

SUBLINGUAL

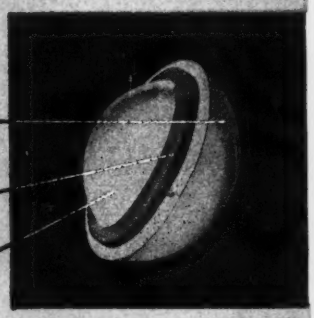
for **Immediate** *relief from anginal pain*

DILCORON contains two highly efficient vasodilators in a unique core-and-jacket tablet.

Glyceryl trinitrate (nitroglycerin)—0.4 mg. (1/150 grain) is in the outer jacket—held under the tongue until the citrus flavor disappears; provides rapid relief in acute or anticipated attack.

The middle layer of the tablet is the citrus "flavor-timer."

Pentaerythritol tetranitrate—15 mg. (1/4 grain) is in the inner core—swallowed for slow enteric absorption and lasting protection.

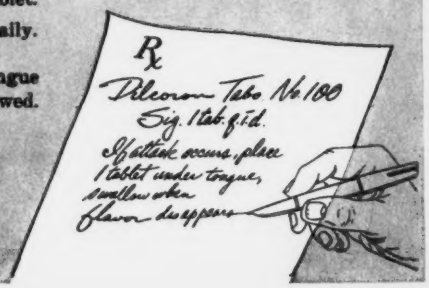


Bottles of 100.

For continuing prophylaxis patients may swallow the entire Dilcoron tablet.

Average prophylactic dose: 1 tablet four times daily.

Therapeutic dose: 1 tablet held under the tongue until citrus flavor disappears, then swallowed.



Winthrop LABORATORIES
NEW YORK 18, N. Y.

improve blood supply

provide prolonged vasodilatation

after a coronary

Improved blood flow to the myocardium, after a coronary thrombosis, promotes development of essential collateral circulation, thereby helping to repair damage.

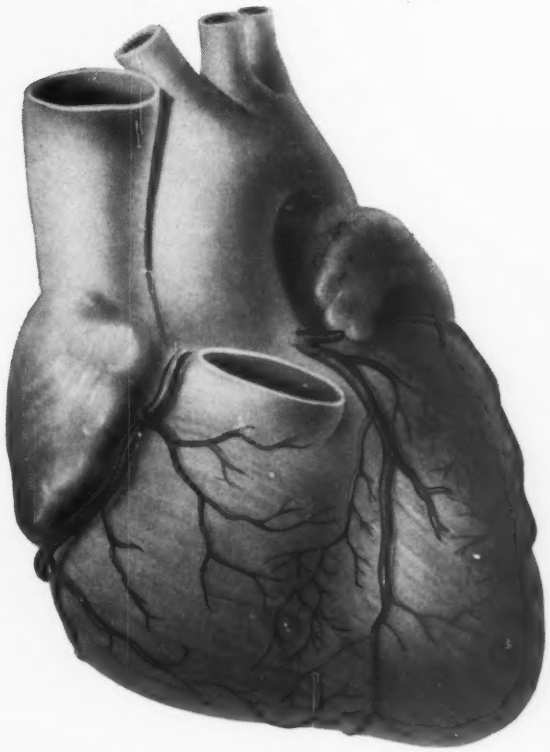
Peritrate, 20 mg. q.i.d., safely increases coronary blood supply without appreciably changing blood pressure or pulse rate. Its routine use in management of the post-coronary patient will provide safe, effective vasodilatation and prevent anginal attacks often encountered in the convalescent period.

Peritrate® 20 mg.

(Brand of pentaerythritol tetranitrate)

WARNER CHILCOTT

MORRIS PLAINS, N. J.



CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

HERRMAN L. BLUMGART, M.D., *Editor-in-Chief*
330 Brookline Avenue, Boston 15, Mass.
EDITH E. PARRIS, Assistant Editor

ASSOCIATE EDITORS

EDGAR V. ALLEN, M.D. *Rochester, Minn.*
STANFORD WESSLER, M.D. *Boston, Mass.*
PAUL M. ZOLL, M.D *Boston, Mass.*

Correspondence concerning *editorial* matters should be addressed to the Editor-in-Chief, at the above address. All communications concerning *business matters*, including *change of address*, should be addressed to the Publisher, Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, N. Y.

Subscription rates, $14.00 per year within the United States and Canada; $15.00 per year elsewhere. Single copies, $2.00; foreign, $2.50. A combination subscription with *Circulation Research* is available at $21.00 per year within the United States and Canada, $23.00 per year elsewhere. Subscriptions are accepted on a calendar year basis.

Agents for Great Britain, H. K. Lewis & Co., Ltd., 136 Gower Street, London, W.C.1, England.

Published monthly at the Publication Office, 120 N. Green St., Chicago, Ill. Second class postage paid at Chicago, Ill.

Original Communications. Manuscripts for publication, letters and all other editorial communications should be addressed to the Editor-in-Chief, at the above address. Articles are accepted for publication on the condition that they are contributed solely to this journal.

Manuscripts. Duplicate manuscripts, tables and illustrations should be submitted to facilitate selection and processing of papers. Manuscripts should be typewritten on good quality paper, one side of the page only, with double or triple spacing and liberal margins. They should include the authors' degrees and hospital and academic affiliations (for use on the "Contributors" page), and an address for mailing proofs. References to the literature should be compiled at the end of the article in numerical sequence, the style of this journal being observed regarding the full amount of material to be included in each bibliographic entry, the order of material, capitalization and punctuation. If a "Personal Communication" is listed in the bibliography, a letter must be submitted in which the direct quotation is given with the signature of the original author.

A foreword not to exceed 100 words should also be submitted with the manuscript. This foreword should serve primarily as an orientation for the reader by stating the general problem, the purpose of the study, and the approach or lines of investigation utilized. The results and conclusions should generally be reserved for the Summary.

Illustrations and Tables. Position of figures and tables in the text should be marked on manuscript. *Circulation* uses arabic rather than roman numbering. Figures should carry their number and the author's name on the back; figure legends should be compiled in a separate list. To ensure clear reproduction, all copy for zinc cuts, including pen drawings and charts, should be prepared with black india ink, and a black ribbon should be used for typewritten material; for halftone work, good photographic prints or the original drawings should be supplied. Special arrangements must be made with the editor for printing of color plates, elaborate tables or an excessive number of illustrations.

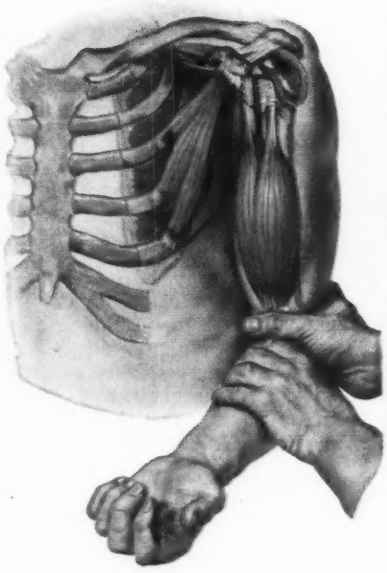
Reprints. Reprints of articles will be furnished to contributors when ordered in advance of publication. An order form, showing cost of reprints is sent with proofs. Individual reprints of an article can usually be obtained by writing directly to its author at the address given on the "Contributors" page of that issue.

Exchanges. Contributions, letters, exchanges, reprints and all other communications relating to the Abstracts Department of *Circulation* should be sent to the Editor-in-Chief at the above address. Writers on subjects which are related in any way to cardiovascular disease are requested to place this address on their permanent mailing list.

Book Reviews. Books and monographs treating specifically of the same subject matter as this Journal will be reviewed as space is available. Send books for review to the Editor-in-Chief, at the above address.

Business Communications. Send all communications regarding advertising, subscriptions, change of address, etc., to the Publisher, at the address listed below. *Remittances for subscriptions* should be made by check, draft, post office or express money order to the Publisher. The Publisher should be advised of *change of address* about thirty days before date of issue, with both the subscriber's old and new address given. *Advertising space* is given only to articles of known scientific value. Forms close first day of month preceding date of issue. Advertising rates and page sizes on application.

COPYRIGHT 1959, GRUNE & STRATTON, INC. 381 FOURTH AVENUE, NEW YORK 16, N. Y.



NEW INDICATION:

Parenteral Priscoline®

relieves bursitis pain

in over 90% of cases[1]

Frankel and Strider[1] report: "Intravenous Priscoline gave excellent to good results in over 90% of our cases."

"Priscoline hydrochloride intravenously is an effective agent in the treatment of acute and recurrent acute subdeltoid bursitis."

The 150 patients in this study were given 1 ml. (25 mg.) Priscoline, by intravenous injection, daily from 1 to 3 days. Excellent results (relief gained immediately or within 24 hours; painless rotation of arm) were achieved in 71 patients. Good results (no sedation required; partial movement of arm without discomfort) were obtained in 68 patients. Eleven patients had no relief.

Patients' ages ranged from 22 to 85 years. Calcification was present in varying degrees in 82 cases. Sixty-nine patients reported previous attacks and had been treated unsuccessfully with X-ray, hydrocortisone and other agents.

The authors suggest it is the sympatholytic action of Priscoline which relieves pain by chemical sympathetic block. Further, "Priscoline may, through its vasodilating ability, promote the transport of calcium away from the bursa."

"We can especially recommend its use in cases where X-ray therapy or local injection of hydrocortisone has failed."

1. Frankel, C. J., and Strider, D. V.: Presented at Meeting of American Academy of Orthopaedic Surgeons, New York, N. Y., Feb. 3, 1958.

SUPPLIED: MULTIPLE-DOSE VIALS, 10 ml., 25 mg. per ml.

Also available: TABLETS, 25 mg.; ELIXIR, 25 mg. per 4-ml. teaspoon.

PRISCOLINE® hydrochloride (tolazoline hydrochloride CIBA)

Illustration by F. Netter, M.D., from CLINICAL SYMPOSIA 10: Cover (Jan.-Feb.) 1958.

2/2587MX

CIBA
SUMMIT, N. J.

CIRCULATION

OFFICIAL JOURNAL OF THE AMERICAN HEART ASSOCIATION

EDITOR-IN-CHIEF

HERRMAN L. BLUMGART, *Boston, Mass.*

EDITH E. PARRIS, *Assistant Editor*

EDITORIAL BOARD

E. COWLES ANDRUS, *Baltimore, Md.*
SAMUEL BELLET, *Philadelphia, Pa.*
RICHARD J. BING, *St. Louis, Mo.*
STANLEY E. BRADLEY, *New York, N. Y.*
HOWARD B. BURCHELL, *Rochester, Minn.*
A. C. CORCORAN, *Cleveland, Ohio*
JEFFERSON M. CRISMON, *San Francisco, Calif.*
MICHAEL E. DE BAKEY, *Houston, Texas*
CLARENCE DE LA CHAPELLE, *New York, N. Y.*
ALBERT DORFMAN, *Chicago, Ill.*
JESSE E. EDWARDS, *Rochester, Minn.*
J. RUSSELL ELKINTON, *Philadelphia, Pa.*
A. CARLTON ERNSTENE, *Cleveland, Ohio*
A. STONE FREEDBERG, *Boston, Mass.*
CHARLES K. FRIEDBERG, *New York, N. Y.*
HARRY GOLDBLATT, *Cleveland, Ohio*
ROBERT P. GRANT, *Bethesda, Md.*
ROBERT E. GROSS, *Boston, Mass.*
HANS H. HECHT, *Salt Lake City, Utah*
EDGAR A. HINES, JR., *Rochester, Minn.*
FRANKLIN D. JOHNSTON, *Ann Arbor, Mich.*
LOUIS N. KATZ, *Chicago, Ill.*
JOHN D. KEITH, *Toronto, Canada*
AARON KELLNER, *New York, N. Y.*
CHARLES E. KOSSMANN, *New York, N. Y.*
WALTER F. KVALE, *Rochester, Minn.*
JERE W. LORD, JR., *New York, N. Y.*
VICTOR A. MCKUSICK, *Baltimore, Md.*
THOMAS M. MCMILLAN, *Philadelphia, Pa.*
DAVID F. OPDYKE, *Jersey City, N. J.*
DICKINSON W. RICHARDS, *New York, N. Y.*
HOWARD B. SPRAGUE, *Boston, Mass.*
FREDRICK J. STARE, *Boston, Mass.*
ISAAC STARR, *Philadelphia, Pa.*
HELEN B. TAUSSIG, *Baltimore, Md.*
JAMES WATT, *Bethesda, Md.*
ROBERT W. WILKINS, *Boston, Mass.*
CHARLES C. WOLFERTH, *Philadelphia, Pa.*
EARL H. WOOD, *Rochester, Minn.*
IRVING S. WRIGHT, *New York, N. Y.*

ASSOCIATE EDITORS

EDGAR V. ALLEN, *Rochester, Minn.*
STANFORD WESSLER, *Boston, Mass.*
PAUL M. ZOLL, *Boston, Mass.*

PUBLICATIONS COMMITTEE, AMERICAN HEART ASSOCIATION

J. SCOTT BUTTERWORTH, *Chairman*, *New York, N. Y.*

WRIGHT R. ADAMS, *Chicago, Ill.*
STANLEY E. BRADLEY, *New York, N. Y.*
LUDWIG W. EICHNA, *New York, N. Y.*
CLIFTON D. HOWE, *Houston, Texas*
PAUL MONTGOMERY, *New York, N. Y.*
JAMES WATT, *Bethesda, Md.*

GEORGE E. WAKERLIN, *Medical Director, American Heart Association, New York, N. Y.*

HERRMAN L. BLUMGART, *Boston, Mass.*
HOWARD P. LEWIS, *Portland, Ore.*
CARL F. SCHMIDT, *Philadelphia, Pa.*

Interlingua Summaries by Science Service, Division de Interlingua, New York, N.Y., ALEXANDER GODE, Chief.

Circulation

FEBRUARY 1959
VOL. XIX NO. 2

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Rheumatic Fever in the Adult: Criteria and Implications

THAT THERE is no specific test for rheumatic fever is well known. This would require no emphasis were it not for the dogmatism with which this diagnosis is often made at the bedside on the basis of nonspecific clinical findings. The report of The Council of Rheumatic Fever[1] entitled "Jones Criteria (Modified) for Guidance in the Diagnosis of Rheumatic Fever" states clearly, "There is no specific laboratory test. The diagnosis must therefore be arbitrary and empirical." In a disease with the serious implications of rheumatic fever, a diagnosis that is necessarily "arbitrary and empirical" calls for caution and restraint, not dogmatism.

This editorial is prompted, in part, by a large and continuing experience with overdiagnosis of rheumatic fever, especially in adults beyond the age of 25. More particularly it is intended to cast doubt on the belief that rheumatic fever in such adults is frequently followed by rheumatic cardiovalvular disease as it is in children. Overdiagnosis is usually due to failure to adhere to established diagnostic criteria such as those of The Council on Rheumatic Fever or to realize the limitations of the so-called major criteria and the nonspecific character of the so-called minor criteria, such as increased erythrocyte sedimentation rate, presence of C-reactive protein, and prolongation of the P-R interval of the electrocardiogram. Diagnostic error has also resulted from equating an elevated titer of antistreptolysin in the serum with active rheumatic fever, instead of limiting its significance to preceding infection with the hemolytic streptococcus.

The diagnosis of rheumatic fever is regarded as highly probable in the presence of at least 2 of the 5 major criteria. Chorea, subcutaneous nodules, and erythema marginatum, which form the 3 most distinctive and specific major criteria, are observed relatively frequently in children with rheumatic fever, but rarely in adults beyond the age of 25. Thus in adults the diagnosis must rest on the basis of the fourth major criterion, arthritis, a nonspecific manifestation of varied cause, and the fifth criterion, carditis, the occurrence of which is difficult to demonstrate in the adult.

In most adults past 25, the diagnosis of rheumatic fever is based on the diagnosis of arthritis alone. Its rheumatic etiology is justified by exclusion of other causes of arthritis, by the therapeutic effect of salicylates on the arthritis and the associated fever, and often also by the history of a preceding sore throat and the presence of a high titer of serum antistreptolysin. But diagnosis by exclusion may be unreliable because it is doubtful that we know all the forms of arthritis or that we can always distinguish the forms that are known. Not very long ago the arthritis associated with disseminated lupus erythematosus without the rash, arthritis associated with erythema nodosum and unrecognized ulcerative colitis, and arthritis associated with periarteritis nodosa or with sarcoidosis, to mention a few exam-

ples, were erroneously diagnosed as rheumatic fever. It is surprising how often a response to salicylates is regarded as convincing evidence of rheumatic fever.

There is inadequate awareness of the tenuous basis on which rheumatic carditis is diagnosed in the adult beyond the age of 25. According to the modified Jones criteria, carditis may be indicated by one or more of the following manifestations, all of which, in my experience are subject to conflicting interpretations:

A. Murmurs: a significant apical systolic murmur, apical diastolic murmur, or basal diastolic murmur, in the absence of previous rheumatic fever or pre-existing cardiovalvular disease; a change in character of the murmurs in individuals with previous rheumatic heart disease. The distinction between a significant and insignificant apical systolic murmur is almost always uncertain, especially during a febrile disease. Yet in practice the diagnosis of rheumatic carditis in adults is most commonly based on the presence of an apical systolic murmur or a presumed alteration in its character. Change in character of the murmur is a matter of subjective interpretation; there is frequent disagreement as to its occurrence. Other factors besides rheumatic valvulitis may account for the change. For these reasons change in the character of a systolic murmur should be abandoned as a criterion of rheumatic carditis. As for a diastolic murmur, its presence in the adult is almost always the result of preceding rheumatic fever and indicates mitral stenosis or aortic regurgitation; at least such an interpretation cannot be excluded.

B. Pericarditis. Since idiopathic pericarditis is being recognized with increasing frequency, the presence of pericarditis can no longer be regarded as specific evidence for rheumatic fever in the adult.

C. Congestive Heart Failure. Most physicians appear to be unaware that the modified Jones criteria quite properly list congestive heart failure as a criterion of rheumatic carditis only in patients below the age of 25. Beyond that age heart failure is most probably due to other causes that cannot be excluded.

D. Increasing Cardiac Enlargement, demonstrated by x-ray examination. In practice this is rarely the basis for a diagnosis of rheumatic carditis in the adult. When it occurs, it is most probably due to a nonrheumatic pericarditis or to congestive heart failure, and the latter cannot be regarded as indicating carditis in the adult. In summary, carditis, which would represent an essential criterion for the diagnosis of rheumatic fever in the adult beyond age 25, is either absent in cases diagnosed as rheumatic fever or it is based on unsatisfactory evidence.

These considerations raise doubt as to the reported frequency of rheumatic fever in the adult who has passed the age of 25. But even if the reported incidence is correct, one may question whether this disease in the adult portends the same dire consequences as in the child or warrants the same measures for prophylaxis and treatment. The clinical importance of rheumatic fever is dependent, not on the arthritis, the chorea, the subcutaneous nodules, and the erythema marginatum, which virtually always subside without residuals, but on the cardiac involvement and the serious consequences of subsequent rheumatic cardiovalvular disease. Rheumatic fever in the child is followed in a large majority of cases by chronic valvular heart disease. In a series of 1,000 cases followed by Bland and Jones,[2] 65.3 per cent had signs of valvular disease on recovery from the initial illness, whereas 44 per cent of the remainder had acquired signs of valvular disease by the end of 20 years. If rheumatic fever in the adult over 25 is to be regarded as an equally significant disease, it must be demonstrated that it, like the disease in childhood, is followed in the majority of cases by chronic rheumatic cardiovalvular disease. In more than 20 years I have never observed a patient with so-called rheumatic fever after the age of 25 who, when first seen, had no history of rheumatic fever or signs of valvular heart

disease and yet subsequently developed signs of chronic rheumatic cardiovalvular disease. In patients with pre-existing valvular disease, evaluation of possible further rheumatic valvular damage is extremely difficult and I have seen no unequivocal example of such an occurrence in the adult.

These experiences have led to the belief that the so-called rheumatic fever in the adult past 25 differs in some essential manner from that in the child or, perhaps more likely, that it differs in failing to elicit the cardiac response, which is the important feature of the disease. The most reliable evidence of significant rheumatic fever is the development of mitral stenosis or aortic regurgitation following the attack, as a rule within 1 or 2 years. Since such a sequence has not been demonstrated in the adult to my knowledge and has not occurred in my experience, it is questionable whether the adult type of arthritis which is termed rheumatic fever should be given this name with its ominous implications of cardiovalvular disease. It may be preferable to diagnose it as idiopathic arthritis or, if it follows a (hemolytic) streptococcus A infection and is associated with a very elevated serum antistreptolysin titer, it may be termed post-streptococcal arthritis.

Follow-up studies have indicated the preeminent importance of the diastolic murmur and the questionable importance of the systolic murmur in both children and adults with rheumatic fever.[3] Sixty-six per cent of 96 children and adolescents without previous heart disease, in whom a definite diastolic murmur appeared or disappeared during the acute attack developed rheumatic heart disease within an average period of 4.8 years. Among 52 similar patients who developed a new, loud apical systolic murmur radiating to the axilla, or a questionable diastolic murmur, only 29 per cent developed rheumatic heart disease. Among adults with an initial attack of so-called rheumatic fever a new diastolic murmur is extremely rare. In many of the cases in which chronic rheumatic heart disease (mitral regurgitation) is diagnosed on the basis of an apical systolic murmur, one may question the diagnosis or the significance of the murmur. Thus, for 391 patients who had been diagnosed as having mitral insufficiency after an attack of rheumatic fever, the over-all annual mortality rate after the age of 20 was 2.76 per thousand which was not significantly different from the death rate of 3.1 per thousand in the United States population as calculated for the same age distribution.[4] The comparable annual death rates for those with mitral stenosis and those with combined mitral and aortic lesions were 7.8 and 29 per thousand, respectively.

Frequently the diagnosis of rheumatic fever or rheumatic activation is made in the adult with rheumatic valvular disease on the basis of fever alone. Thus an erroneous diagnosis of rheumatic fever was commonly made in cases of bacterial endocarditis. In many patients with mitral stenosis who were awaiting operation mitral commissurotomy was denied or delayed too long because the presence of fever was wrongly interpreted to signify active rheumatic fever. In most such cases the fever was due to pulmonary embolism, patchy bronchopneumonia, or to viral bronchopulmonary infection. The development or progression of heart failure in the adult with rheumatic heart disease is often attributed to active rheumatic fever, especially if the patient is febrile. These diagnostic concepts are based on the traditional teaching that rheumatic fever is a persistent, chronic disease with a tendency to recrudescence throughout life. This teaching in turn was based on postmortem findings of Aschoff bodies in the myocardium of patients in the third to sixth decades who died of rheumatic heart disease and heart failure long after the overt, acute attacks of rheumatic fever. The Aschoff body was interpreted to signify active rheumatic fever. This interpretation and the concepts based on it are no longer tenable, since biopsy specimens of left atrial appendages have disclosed a high incidence of Aschoff bodies, without relation to the clinical picture and subsequent course, leading to the conclusion that the presence of Aschoff bodies cannot be regarded as evidence of

clinically active rheumatic fever. If further studies support evidence that there are fresh and senescent Aschoff bodies that can be differentiated by special stains,[5] the fresh Aschoff body may be found to be acceptable as a pathologic criterion of clinically active rheumatic fever.

In conclusion, it is emphasized that rheumatic fever is a disease whose clinical and public health importance is based on the subsequent development, in about 75 per cent of cases, of mitral stenosis, aortic insufficiency, or both. In adults beyond the age of 25, rheumatic fever is rare when judged by this criterion of subsequent valvular disease. In such adults rheumatic fever should be diagnosed only when 2 of the major criteria of Jones (modified) are present, which mean essentially arthritis and carditis, but carditis in the adult should be diagnosed only on the appearance of a diastolic murmur not previously present. When nondeforming, febrile polyarthritis occurs without carditis in the adult after a streptococcus A infection, when it is associated with a high serum antistreptolysin titer, when it promptly responds to salicylate therapy, and when other causes of arthritis are excluded, it should be termed post-streptococcal arthritis, not rheumatic fever, because mitral stenosis and aortic regurgitation rarely if ever follow such arthritis. In order to avoid errors in diagnosis and treatment, unexplained fever, pericarditis, or congestive heart failure in adults with rheumatic heart disease should rarely if ever be attributed to activation of rheumatic fever. There is need for follow-up study of adults who experience their first attack of so-called rheumatic fever after the age of 25. If it can be demonstrated that the characteristic valve lesions follow post-streptococcal arthritis in adults as frequently as in children, the traditional concept of rheumatic fever can be re-instated. But in the absence of such evidence the serious prognosis with respect to subsequent cardiac disturbance, the prolonged inactivation, and the continuous prophylactic therapy for rheumatic fever in childhood do not appear warranted in the adult past the age of 25.

CHARLES K. FRIEDBERG

1. COUNCIL OF RHEUMATIC FEVER OF THE AMERICAN HEART ASSOCIATION: Jones criteria (modified) for guidance in the diagnosis of rheumatic fever. Modern Concepts Cardiovasc. Dis. **24**: 291, 1955.
2. BLAND, E. F., AND JONES, T. D.: Rheumatic fever and rheumatic heart disease. A twenty year report on 1,000 patients followed since childhood. Circulation **4**: 836, 1951.
3. FEINSTEIN, A. R., AND DIMASSA, R.: The prognosis of rheumatic carditis. Clin. Research **6**: 220, 1958.
4. WILSON, M. G., AND LIM, W. N.: The natural history of rheumatic heart disease in the third, fourth, and fifth decades of life. I. Prognosis with special reference to survivorship. Circulation **16**: 700, 1957.
5. TEDESCHI, C. G., WAGNER, B. M., AND PANI, K. C.: Studies in rheumatic fever. I. The clinical significance of the Aschoff body based on morphologic observations. Arch. Path. **60**: 408, 1955.

Sydenham was called 'a man of many doubts,' and therein lay the secret of his great strength.—WILLIAM OSLER, M.D. *British Medicine in Greater Britain.* Montreal Med. Journal, 1897.

Clinical Study of Twenty-Three Cases of Ebstein's Anomaly of the Tricuspid Valve

By GEROLD L. SCHIEBLER, M.D., PAUL ADAMS, JR., M.D., RAY C. ANDERSON, PH.D., M.D., KURT AMPLATZ, M.D., AND RICHARD G. LESTER, M.D.

The clinical findings in 23 cases of Ebstein's anomaly are presented, together with a discussion of the diagnostic and surgical aspects of this defect. Attention is again drawn to the frequent occurrence of the Wolff-Parkinson-White electrocardiographic pattern in this anomaly.

IN 1937 Yater and Shapiro[1] reported a case of Ebstein's anomaly of the tricuspid valve from this hospital. No further cases were recognized by our group until 1951, when we identified case 18 in the present series on the basis of Taussig's[2] description of this anomaly. Since then, we have come to recognize this defect with increasing frequency, and have now studied a total of 23 cases apart from the case of Yater and Shapiro. Eight of these have had postmortem studies. All patients were examined by the staff of the University of Minnesota Hospitals.

As originally described almost a century ago,[3] the sine qua non of this valvular malformation is that a portion or all of the leaflets of the tricuspid valve are displaced downward from the anatomic annulus separating the right atrium and the right ventricle. This defect has become a well recognized clinical entity. Our case material covers a wide spectrum of clinical symptomatology and anatomic variety, thereby allowing a fairly comprehensive treatment of the subject.

INCIDENCE

The world literature now contains more than 140 cases of Ebstein's malformation, and the rapidity with which new cases are being reported indicates that this anomaly is not uncommon. Maude Abbott's[4] review of 1,000 autopsied congenital heart lesions contained at least 1 case. Keith and co-workers[5] suggested an incidence figure of 1:210,000 live births, and found this defect to constitute less than 1 per cent of all congenital heart defects.

SEX RATIO

Our series consists of 10 females and 13 males, supporting the current concept that there is an equal sex ratio in this entity.

PRENATAL HISTORY

Information on this subject was available in 19 of the 23 cases. In 12 of these, the pregnancy was "uneventful" or "uncomplicated." The other 7 reported the following incidents during pregnancy: nausea and vomiting in the first trimester with transient bleeding in the sixth month (case 2), marked hypertension and premature labor preceded by hemorrhage (case 3), exposure to mumps during the seventh month of gestation (case 4), hyperemesis gravidarum during the entire gestational period (case 8), transient uterine bleeding in the third month (case 9), malaria during the sixth week (case 10), and exposure to measles during the third month with a "few red spots on the arms" (case 12). In the absence of control data, it is not possible to evaluate the etiologic importance of these incidents.

FAMILY HISTORY

There have been no reports in the literature of multiple cases of Ebstein's anomaly in the same family. Grob et al.[6] stated in their case report that "a cousin of the child's mother" had acyanotic congenital heart disease. Blount et al.[7] and Bayer et al.[8] reported cases that had a normal nonidentical twin. Blacket et al.[9]

From the Departments of Pediatrics and Radiology, University of Minnesota Hospitals, Minneapolis, Minn.

This study was aided by a grant from the Minnesota Heart Association, and in part by a research grant from the American Heart Association.

TABLE 1.—*Symptoms in Patients Surviving the Neonatal Period (18 patients)*

Symptom	Number	Remarks
Dyspnea	18	None with orthostatic dyspnea[27]
Cyanosis	15	One of these (case 2) had a closed foramen ovale
Excessive fatigue	13	
Neurologic symptoms	11	Syncope in 5 (2 with exertion, 2 with paroxysmal tachycardia, and 1 at rest); thromboembolic phenomena in 2; febrile convulsions in 3; "dizzy spells" in 1; transient visual loss in 1
Cardiac failure	9	Later or terminally in 6; with paroxysmal tachycardia in 2; with nephrosis in 1
Precordial or epigastric pain	7	With exertion or emotional stress in 4, and with paroxysmal tachycardia in 3
Paroxysms of tachycardia	7	Between paroxysms 4 had sinoatrial rhythm; 3 had the W-P-W pattern. Case 5 had paroxysm of tachycardia at catheterization only
Squatting	5	With exertion in 4; with paroxysmal tachycardia in 1
Headaches	5	All with emotion or exertion
Protracted cough	4	In 3 after a bout of exertion
Photophobia	3	
Failure to gain weight	2	

reported a patient whose older brother was known to have heart disease and died suddenly at the age of 17 while playing tennis.

Detailed family information was available in 22 of our cases. There were no cases of congenital heart disease among the 44 parents and 53 siblings. One patient (case 7) had a maternal first cousin, once removed, who was shown to have a ventricular septal defect by cardiac catheterization. Otherwise, there were no known relatives with congenital heart disease. None of the cases was a member of twin pairs.

There appeared to be no significant relationship to birth order, birth weight (none was premature by weight), age of mother, or month of birth (though 14 were born in the 6 month period from September to February, 5 being in December). However, the series is so small that these features cannot be properly evaluated.

Neonatal Symptoms and Signs

Twelve of our cases had symptoms or signs of congenital heart disease during the neonatal period.

Seven of our 8 autopsied cases fell into this category. In 5, a murmur and cyanosis were noted at birth or shortly thereafter, 1 (case 1) dying in 26 hours of severe cardiac failure. Another showed only a murmur, and the last displayed cyanosis and "sluggishness" at birth and a paroxysm of supraventricular tachycardia at several weeks of age.

Five of our living patients (data available on the neonatal period in 13) had either a murmur or cyanosis or both during the neonatal period. In all, the neonatal cyanosis decreased or disappeared with the passage of time, but recurred later in life.

Numerous authors[5-26] have described cases with Ebstein's defect with neonatal difficulties. Five cases dying in the first few days of life have been reported.[5, 14, 21, 25] The cyanosis at birth and its gradual disappearance have been noted by Engle et al.[22] and Kilby et al.[13] This transient cyanosis may represent a right-to-left shunt through the foramen ovale secondary to normal high pulmonary bed resistance in the presence of a poorly functioning right ventricle. The cyanosis may then disappear or decrease with the normal drop in pulmonary resistance in early infancy. In addition, the normal decrease in hemoglobin level after birth may diminish the degree of cyanosis, so that the improvement may be more apparent than real. Unrecognized bouts of paroxysmal supraventricular tachycardia with spontaneous reversion may account for some cases of transient cyanosis.

Symptoms after the Neonatal Period

Twenty-two patients survived the first month of life. Four of these (ranging in age from 4 to 11 years, cases 9, 10, 11, and 15) are

currently asymptomatic. Of the remaining 18 patients, 11 had symptoms in the neonatal period; in the others the onset of symptomatology was vague and indefinite. In case 23 symptoms first developed at 30 years of age. As shown in table 1, dyspnea, cyanosis, and excessive fatigue were the most common symptoms.

Physical Findings

Physique. The values for height and weight were plotted on the Iowa grid, with serial measurements available in most of the children. Six patients were above the 85th percentile for both height and weight; 5 were below the 16th percentile; and 8 were between these limits (table 2). Thus, as a group, patients with this cardiac malformation show normal growth features. This is particularly true if cyanosis is absent, since none of the acyanotic patients was below the 16th percentile. Patients seen initially as adults had a normal weight for their age and height.

Skin Color. Seven patients have shown no cyanosis of the skin or mucous membranes at any time. One patient (case 2) showed cyanosis only terminally, 3 had cyanosis only with exertion, and 12 had cyanosis at rest. All living patients who had cyanosis in the neonatal period improved transiently, but now have cyanosis at rest or with exertion. As Engle et al.[22] reported originally, cyanosis is not closely correlated with exercise tolerance. Thus, 2 of our severely cyanotic adults do manual labor without difficulty, while 1 of our acyanotic adults (case 23) has definitely decreased exercise tolerance.

Unusual facial colorations such as "violaceous hue,"[7, 8, 12] "flushed,"[7] "florid,"[9, 28] and "red-cheeked"[9, 29] have been described in patients with Ebstein's anomaly. Similar observations have been made in our cases, often prior to the establishment of the correct diagnosis. In our 23 cases, 10 showed a peculiar facial coloration, which may have diagnostic significance somewhat akin to the "malar flush" of mitral stenosis.

Clubbing of the fingers was present in 6 patients, all cyanotic.

Table 2.—*Physical Findings in Ebstein's Anomaly —Twenty-Three Cases*

Systolic murmur	23	
P_2 equal or greater than A_2	23	
Lungs clear to auscultation	23	
Cardiomegaly	21	
Normal physique	18	
"Triple" or "quadruple" rhythm	18	
Cyanosis	16	(13 at rest, 3 only with exertion)
Systolic thrill	15	
Diffuse point of maximal impulse	13	
Diastolic murmur	11	
"Split" first sound	11	(Some had a systolic ejection "click")
"Metallic" or "clicking" heart tones	10	
"Facial erythema"	10	
Cardiac failure	9	
Normal chest contour	9	
Dyspnea at rest	8	(6 terminal, 2 with paroxysms of tachycardia)
Localized point of maximal impulse	6	
Clubbing	6	
Left chest prominence	6	
Bilateral chest prominence	5	
Visible thrust of chest	5	
Observed paroxysms of tachycardia	5	(2 at catheterization)
"Fair" or "weak" peripheral pulses	5	
Pericardial friction rubs	3	

Chest Shape and Auscultation of the Lungs. Information on chest shape is available in 21 of our 23 cases. Nine had a normal chest contour. Five were considered to have an increase in the anteroposterior diameter with bilateral chest prominence; 6 were reported to have left chest prominence; and 1, right chest prominence. Acyanotic patients invariably had a normal chest contour.

In no case, even when cardiac failure was present, were rales heard in the chest.

Peripheral Vessels. The peripheral vessels were usually described as normal, although in 5 of the cyanotic patients the pulses were noted to be "fair" or "weak." Blood pressures in the arms and legs were found to be within normal limits, except in 1 adult (case 20) whose systolic arm pressure was 160 mm. Hg. In measuring the blood pressure, the diastolic end point was sometimes difficult to ascertain, particularly if the patient was cyanotic or in heart failure. Similar observations have been made by Blacket et al.[9] and Kilby et al.[13]

In general, no specific observations were made regarding the neck veins. There was a definite presystolic pulsation of the neck vessels associated with tricuspid insufficiency in case 7, who was in severe congestive failure. However, pulsations of the liver were not noted. In 1 of our asymptomatic patients (case 9), a phlebogram showed evidence of tricuspid insufficiency.

Cardiac Findings. Five of the patients had a visible thrust of the precordium. The point of maximal impulse was described in 19 cases. In 13 it was "diffuse," but in the others it was "localized." These observations could not be correlated with heart size.

A systolic thrill was noted in 15 of the 23 cases at the lower left sternal border or at the "apex." In several cases the thrill was maximum over the displaced tricuspid valve as determined at cardiac catheterization. We agree with Blount et al.[7] that the "apex" represents the location of the tricuspid valve in an enlarged heart with leftward displacement of the valve. No diastolic thrills were noted. The intensity of the systolic thrill was poorly correlated with heart size, but was more prominent in the presence of cardiac failure. During open heart surgery in 2 patients (cases 6 and 7), the thrill was felt over the huge right atrium during ventricular systole. Tricuspid valvular insufficiency was identified by direct observation.

The heart rate varied normally with age, except during episodes of paroxysmal tachycardia. In only 3 cases was marked sinus arrhythmia noted (cases 10, 19, and 23).

The heart sounds were variable. Soft and diminished heart sounds have been emphasized to be of diagnostic significance.[9, 22] We have found this feature only in a minority of cases, the heart sounds usually being of normal intensity. "Metallic" or "clicking" heart tones were described in 10 patients. The "triple" or "gallop" rhythm so frequently described in the literature was noted in 18 of our 23 cases, and in 6 of these the rhythm was recorded as "quadruple." The triple rhythm is produced by a low frequency early to mid-diastolic third heart sound or soft murmur, usually maximal along the lower left sternal border or the "apex." The "quadruple" rhythm is caused by an additional presystolic sound or murmur.

The first sound was noted to be "split" in 11 of the patients. Characteristically, the second portion of the split first sound was louder than the first portion, suggestive to some observers of a systolic ejection click. Also, the widely split first sound plus a second and third heart sound led to the occasional description of a "quadruple" rhythm. In children the second sound over the pulmonic area was usually described as "split" and louder than over the aortic area. In adults, the second sound over the pulmonic area was usually noted to be pure and equal in intensity to that over the aortic area. In *no case* was the second sound described as being diminished over the pulmonic area.

All our cases had a systolic murmur, although in 1 patient (case 2) it was not noted until 16 months of age. The maximal intensity of the murmur was always noted to be at the lower left sternal border, or from there to the "apex." Again, we think that the location of the murmur depends upon the location of the tricuspid valve. The majority of the murmurs were of grade II to III intensity, but varied from a barely audible grade I murmur to the grade V murmur. The intensity had no close relationship to heart size, but appeared to increase with cardiac failure. The quality of the murmur was also variable, only rarely being described as "coarse" or "scratchy."

As previously noted, 18 of our cases had diastolic sounds. Eleven of these represented a discrete murmur, varying from protodiastolic to presystolic in time, and variable also in intensity and quality. The usual location and greatest intensity were at the lower left sternal border or just to the left at the "apex." These diastolic sounds and murmurs were usually accentuated in the inspiratory phase of respiration, thus suggesting a tricuspid valve origin.

A to-and-fro murmur was described in 3 of our cases, as well as by others.[5, 13, 22] One of these (case 17) is still living; in the other 2 patients (cases 4 and 7) postmortem examination showed pericardial effusion and fibrinous pericarditis. This combination of pericarditis and pericardial effusion, often bloody, has been noted by others,[18, 30, 31] and has been attributed to extravasation of blood from the coronary veins because of increased venous pressure. On the basis of these observations, we believe that the to-and-fro murmurs in our cases were actually pericardial friction rubs.

Routine Laboratory Findings

The hemoglobin, erythrocyte count, and hematocrit were elevated in the cyanotic cases. Albuminuria was noted in individuals with cardiac failure and in the single patient in whom typical nephrosis was associated with Ebstein's anomaly. Otherwise, routine laboratory studies were normal.

Roentgenographic Findings

We have found considerable variation in the cardiac contour on roentgenograms in patients with Ebstein's anomaly (figs. 1 and 2). In 4 instances we have obtained roentgenograms within the first few days of life. In case 1 the heart was markedly enlarged at 5 hours of age, while in the others (cases 2, 3, and 12) the heart contour was within normal limits.

In the majority of our cases the cardiac contour could be loosely grouped into 2 types. One group showed moderate cardiomegaly and a contour simulating left ventricular enlargement in both the anteroposterior and left oblique views. Several of these were at first mistakenly diagnosed as mild aortic stenosis. The other group showed marked cardiomegaly and a boxlike contour. When this contour is present, it is highly diagnostic of Ebstein's defect; it is due to an almost horizontal takeoff of the left border of the heart near the aorta, sometimes extending virtually to the left chest border. Right atrial enlargement, leading to enlargement of the upper right border, may also contribute to this squarish appearance. The bulging of the upper left heart border is probably due primarily to the displacement of the infundibulum of the right ventricle by the markedly enlarged right atrium, and to a lesser degree by dilatation of the outflow tract of the right ventricle. This same contour may be encountered in patients with valvular pulmonic stenosis and cardiac failure, rheumatic heart disease, or total anomalous pulmonary venous connection to the right atrium.

The contours in some of our other cases resembled those seen in tetralogy of Fallot, tricuspid atresia, pulmonary atresia, or isolated pulmonary valvular stenosis.

In case 2 no definite cardiomegaly occurred prior to her death with nephrosis at 2½ years. Individuals with this malformation having a normal-sized heart have been reported by several writers.[2, 16, 26, 32–34]

The pulmonary vascular markings were always normal or decreased. A close correlation exists between the degree of cyanosis and the decrease in the vascular markings. Even in cases with cardiac failure there was no increase in pulmonary vascular markings and no evidence of pleural effusion. The main pulmonary artery segment was often difficult to identify, and the aortic knob generally appeared small. However, both may be totally or partially obscured by the right-sided chamber enlargement. *None* of our cases showed roentgenographic evidence of left atrial enlargement, a very helpful sign in the exclusion of mitral valve lesions. Calcifications in the atrioventricular ring may appear both in Ebstein's defect[35] and in rheumatic heart disease.

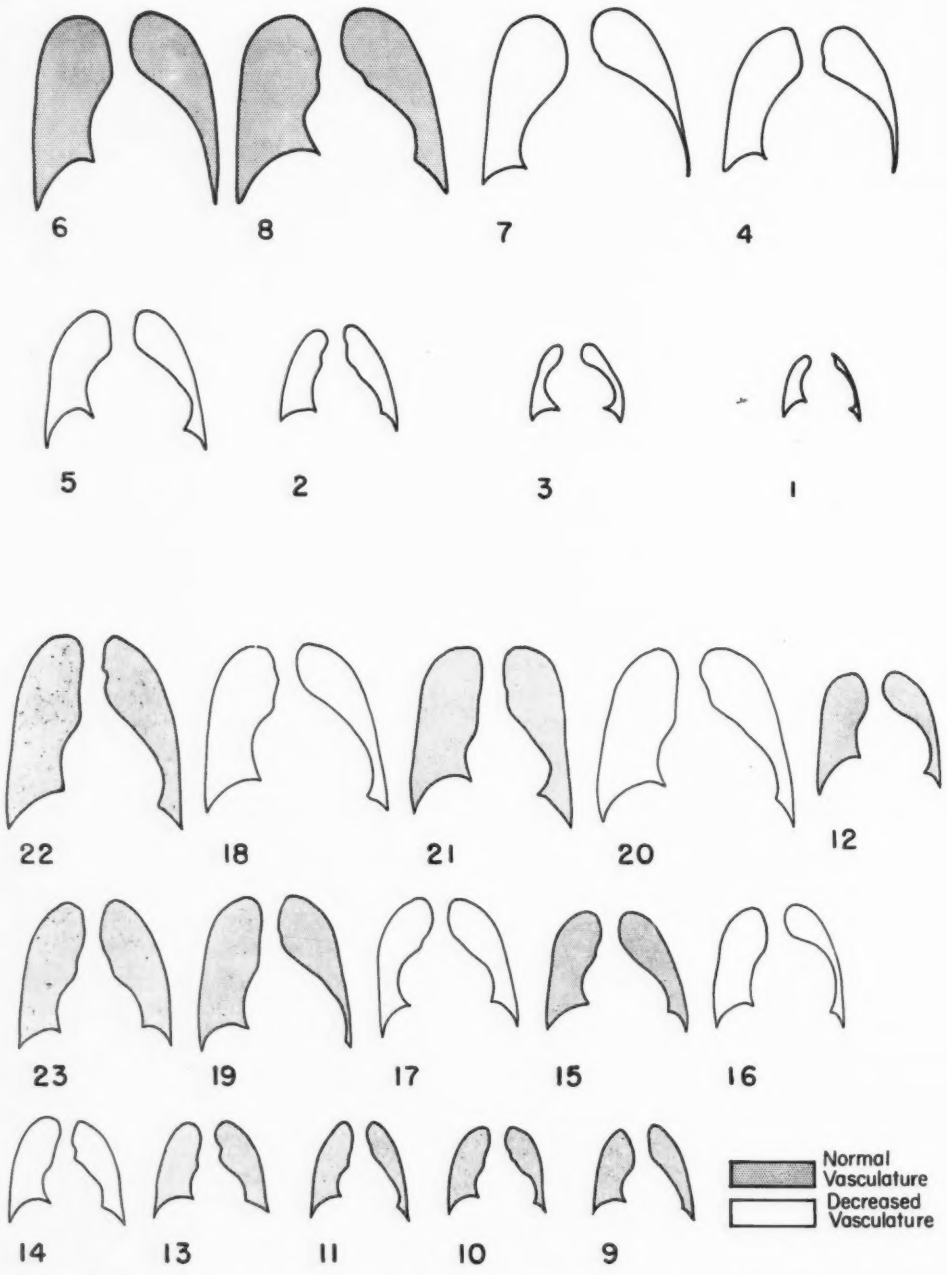


FIG. 1 *Top.* Tracings of chest roentgenograms of autopsied cases to show cardiac contour and pulmonary vasculature. *Numbers* refer to case numbers.

FIG. 2 *Bottom.* Tracings of chest roentgenograms of living patients to show cardiac contour and pulmonary vasculature.

Kymography showed the pulsations of the right side of the heart to be increased in some cases, and normal or decreased in others. They were not consistent enough to be of much diagnostic aid.

A more detailed report of the roentgenographic aspect of Ebstein's anomaly is being published separately.[36]

Angiocardiography

Angiocardiography was performed here in cases 14 and 19 and elsewhere in case 6. Though our experience is limited, we agree with Kjellberg et al.[37] that peripheral angiocardiography is probably of very limited value, inasmuch as the contrast medium is so diluted in the large right atrium that anatomic details are difficult to visualize. Also, its potential danger to the patient[12, 14] undoubtedly outweighs its diagnostic usefulness. On the other hand, selective angiocardiography performed from the right ventricle might be useful in delineating the anatomic features of the right ventricle, but we have not done such a procedure in any of our cases.

Electrocardiographic Findings

A. *Without Wolff-Parkinson-White Pattern (Table 3)*

Seventeen of our patients did not show the Wolff-Parkinson-White (W-P-W) pattern at any time, while 1 was variable in this respect. We have carried out a separate, detailed analysis of the electrocardiograms in these 18 cases (8 of whom had 2 or more tracings). All subsequent comparisons for children are stated in relation to Ziegler's[38] normal values.

The QRS axis was calculated on the basis of both area and voltage. The highly notched, slurred, and splintered QRS complexes make axis determination very difficult. The axis based on voltage is probably not meaningful, but that based on area may have greater significance. In our cases, the axis was usually right (including $S_1S_2S_3$ patterns), but several cases showed either a normal or left axis.

The rhythm was usually sinoatrial, except for occasional atrioventricular nodal rhythm in case 19; and whenever sinoatrial bradycardia (under 60) was present, cases 8 and 13 developed atrioventricular dissociation. Only occasional nodal or ventricular premature beats were noted.

Six of the children showed a prolonged P-R interval. None of the children under 16 had a consistently normal QRS pattern during the course of the clinical observation; 2 children (cases 2 and 11) were initially normal and progressed to an incomplete right bundle-branch block. Another (case 9) progressed from an incomplete to a complete right bundle-branch block. Of the 5 patients over 16 years of age, 4 showed right bundle-branch block, and the other had a normal QRS with sinoatrial rhythm and complete right bundle-branch block when nodal rhythm supervened. The right bundle-branch block configuration was frequently atypical.

The uncorrected Q-T interval was normal in all but 3 patients. Case 1 had a prolonged Q-T for age and rate; cases 6 and 17 developed a prolonged Q-T interval as demonstrated by serial electrocardiograms. These latter 2 cases showed gradual prolongation of the P-R interval and the QRS duration, so that the prolonged Q-T may have been due to the long QRS.

Of the 18 cases, 14 showed maximum or higher than normal P waves, the peaking always occurring in V_2 and V_3 if present at all. There was prominent notching or slurring of the P wave in only 4 cases.

The duration of the P wave was increased in 3 adults and 5 children. Van Lingen and Baversfeld[39] postulated that the increase in the P-R interval was caused by an increase in the duration of the P wave, and that the P-R interval per se was not increased. Only 3 of our 6 cases with a prolonged P-R interval, however, had a P wave of abnormal duration.

The 4 children showing both an increase in height and duration of the P wave have all died, while the 2 adults with these features are living. The 4 patients who have normal P waves in all leads are still living and relatively asymptomatic. Those 3 patients whose only abnormality is an increased height of the P wave in the precordial leads are only mildly symptomatic. Patients showing abnormally

TABLE 3.—*Electrocardiograms without W-P-W Pattern*

Case no.	Age	Axis* Voltage	Axis* Area	Rate	Rhythm	P-R interval lead II	QRS lead II	Height of P in lead II	Max. duration P in leads I, II, III	Height of P in V_2	V_1 pattern	Highest R/S in V_1	Intrinsicoid deflection V_1	V_6 pattern
1	5 hr.	+100	+110	140	Sinus	0.14	0.11	3.0	0.07	3.0	rsR′	8/4	0.08	RS
2	1 mo.	+180	+170	300	SVT	—	0.04	—	—	—	rS	1.5/6	0.025	rs
	5 mo.	—150	+150	145	Sinus	0.12	0.07	3.5	0.07	3.0	rS	5/8	0.015	RS
	2 yr.	—110	+110	115	Sinus	0.14	0.09	4.0	0.07	4.0	rsr′s′	1.5/1.8	0.04	qrS
4	5 yr.	—150	—170	107	Sinus	0.17	0.11	2.5	0.10	4.0	rsr′	3.3/2.2	0.08	rsR′s′
	10 yr.	+180	+180	110	Sinus	0.22	0.13	4.5	0.09	3.5	r	3/0	0.09	rsr′S′
5	9 yr.	+100	+120	130	Sinus	0.16	0.10	3.5	0.08	6.0	rsr′s′	2.5/1	0.06	RS
6	6 yr.	—45	—140	115	Sinus	0.20	0.12	5.0	0.09	4.0	rsr′	5/3.5	0.10	qRS
	13 yr.	—100	—135	95	Sinus	0.22	0.18	7.5	0.11	5.0	rsR′	6/2.8	0.12	qRS
7	14 yr.	+120	+140	115	Sinus	0.20	0.15	4.5	0.12	5.0	rsr′	3.5/0.8	0.12	rsR′S′
8	13 yr.	+30	+105	70	Sinus or A-V dissociation	0.18	0.13	3.0	0.10	4.0	rsR′	7/3	0.075	qRs
9	11 mo.	+75	+100	120	Sinus	0.13	0.09	1.5	0.08	1.5	rsR′	7/2.5	0.06	qRs
	4 yr.	+90	+100	85	Sinus	0.14	0.10	0.5	0.08	1.0	rsr′s′	5/5	0.06	qRs
11	2 yr.	+110	+130	130	Sinus	0.16	0.08	2.5	0.08	3.0	qrs	4.5/3	0.035	qRs
	6 yr.	+110	+120	105	Sinus	0.18	0.09	1.4	0.09	3.5	qrS	2.3/5.5	0.035	qRS
13	8 yr.	—40	—80	65	Sinus or A-V dissociation	0.15	0.13	1.0	0.09	0.5	rS	3.4/8.5	0.02	qRs
15	9 yr.	—20	—150	75	Sinus	0.15	0.13	1.0	0.10	1.5	rsR′	7/5	0.07	qRs
16	6 yr.	—40	—20	100	Sinus	0.12	0.10	3.0	0.09	3.5	rs	0.4/4	0.02	qRs
	12 yr.	+15	—35	90	Sinus	0.14	0.10	4.5	0.09	4.0	rsr′	0.4/4.5	0.10	Rsr′s′
17	6 yr.	—60	—145	100	Sinus	0.19	0.12	2.5	0.09	—	—	—	—	—
	13 yr.	—25	+180	70	Sinus	0.23	0.20	2.5	0.09	2.5	rsr′s′	4/2.8	0.01†	qRs
19	15 yr.	+110	+110	85	Nodal	—	0.13	—	—	—	—	—	—	—
	20 yr.	+105	+110	90	Sinus	0.21	0.09	3.0	0.11	2.5	rsr′s′	2/2	0.055	Rsr′
20	28 yr.	+130	+140	95	Sinus	0.17	0.13	3.5	0.11	5.0	rsR′s′	8/4	0.055	Rs
21	35 yr.	—30	+20	80	Sinus	0.20	0.14	1.5	0.09	2.0	rsr′	4/4	0.10	qRs
22	36 yr.	+150	+170	75	Sinus	0.21	0.13	1.5	0.11	4.0	rsr′	4/3	0.11	qRs
23	35 yr.	+60	+45	80	Sinus	0.18	0.12	0.5	0.10	1.0	rsr′	3/0.8	0.07	qrs

*Maximum instantaneous voltage and area of QRS were used for 2 independent determinations.

†Intrinsicoid deflection in V_1 0.07 second on tracing taken at the age of 9.

high P waves in 8 or more of the standard electrocardiographic leads tended to have more severe symptoms or early death.

Notching or slurring of the QRS complexes was present in 1 or more leads of all patients. Lead I generally showed an rS pattern, lead II usually a qRs pattern, and lead III a QR or QRS pattern. Van Lingen's[39] observation, that an R plus S voltage less than 7 mm. in the standard leads was of diagnostic value in this entity, was confirmed in 4 of the 5 adult cases, but was present in only 6 of the 13 children. That these complexes may change with time was shown by serial electrocardiograms in which there was often a progressive decrease in the voltage and an increase in the amount of notching or slurring as the child grew older.

In V_1 the pattern was usually rS or occasionally qrs, both with wide splintering. The tallest R wave encountered in lead V_1 in all tracings was 8 mm. This observation agrees well with that of Keith et al.[5] who found that the tallest R wave in V_1 was 7 mm. or less except in 1 case where it was 9 mm. A pattern of right ventricular hypertrophy was not seen in V_1 in any patient. However, right ventricular hypertrophy in this malformation has been reported by others.[7, 14, 37, 40] In all but case 13 the ventricular activation time (intrinsicoid deflection) was 0.04 second or greater in V_1. However, in 2 patients the progression from normal to prolonged time was noted during the course of our observations.

In V_6, about one half the tracings showed no q wave, probably due to the displacement of the left ventricle by the large dilated right atrium. In these, a q wave could be seen in leads taken further to the left (V_7 to V_9). In only 1 (case 15) was the intrinsicoid deflection delayed in V_6 when a q wave was present. No left ventricular hypertrophy patterns were noted.

The ST-segment changes were nonspecific and nondiagnostic. Slight depression or elevation in leads II, III, aV_F, slight elevation in V_1, and slight depression in V_6 were occasionally seen.

The T waves were normal, except that in leads II, III and aV_F, the incidence of diphasic or negative T waves appeared to be somewhat greater than might be expected. This was probably largely positional artefact, caused by the huge right atrium and an enlarged heart. Seven patients had diphasic T waves in V_5 and 2 of these in V_6, probably for the same reason. This view is supported by the finding of normal T waves in leads V_7 to V_9 where the QRS complex is initiated with a q wave.

In summary, our findings are very similar to those reported previously, the typical features being (1) incomplete or complete right bundle-branch block, with widely splintered, notched, and slurred QRS complexes, (2) increased height and, on occasion, duration of the P wave, (3) low voltage in the right precordial leads, with the tallest R wave in V_1 not exceeding 8 mm., and (4) right axis deviation. Also encountered were a prolonged P-R interval, nonspecific ST-segment changes, bouts of supraventricular tachycardia, atrioventricular dissociation, premature beats, and a normal or left axis.

Sodi-Pallares[41] has stated that the diagnosis of this cardiac anomaly must be strongly considered if the electrocardiogram shows a QR pattern and negative T waves from V_1 to V_4 or V_6, particularly if found in a young person with cyanosis. In our review, we have found no case fitting these criteria. One of our patients (case 11) on a single tracing has a QR pattern all across the precordium with negative T waves from V_1 to V_4, but she is not cyanotic. Two others, with cyanosis or oxygen desaturation, had a QR pattern in leads V_{4R} or V_1, with a negative T wave, but this pattern did not extend to V_2. Thus in our experience, this pattern is not of diagnostic usefulness.

Michel et al.[42] proposed that the broad R′ deflection of low amplitude in leads II and III, following a normally shaped R wave, represented the delayed activation of the atrialized portion of the right ventricle. They suggested that these be called P′ waves because of their similarity to the P waves. Only 3 of our patients (cases 4, 7, and 17), show a pattern similar to this description. In 2 of these, serial tracings clearly demonstrate that this pattern develops with time and with increase in the notching and slurring of the QRS complexes. Even though Michel et al.[42] found this in 2 of their cases, and in 6 of 9 cases they reviewed from the literature, in our experience this finding has little diagnostic significance.

B. With Wolff-Parkinson-White Pattern (Table 4)

We have found the W-P-W electrocardiographic pattern in 6 of our 23 cases, and believe that this finding deserves special emphasis. Sodi-Pallares[41] first drew attention to this unique association, and interpreted the electrocardiogram of Yater and Shapiro[1] as being a W-P-W pattern. We have reviewed

TABLE 4.—*Electrocardiograms with W-P-W pattern*

Case no.	Age	Axis		Rate	Rhythm	P-R interval lead II	QRS lead II	Height of P in lead II	Max-duration P in leads I, II, III	Height of P in V_2	V_1 pattern	Highest R/S in lead V_1	Intrinsicoid deflection V_1	V_6 pattern and R/S ratio	
		Voltage	Area												
3	1 mo.	—40	—50	170	Sinus	0.06	0.09	1.5	0.06	1.7	rS	5/20	0.03	Rs	11/4
	3½ mo.	—70	—95	170	Sinus	0.06	0.09	5.0	0.06	3.0	rS	4/6	0.03	RS	16/11
6	10 yr.	—35	—40	75	Sinus	0.14	0.18	3.8	0.10	5.0	rS	1/9	0.02	RsR's'	7.5/4/6.5/3
10	3 yr.	—30	—30	105	Sinus	0.08	0.11	1.0	0.07	2.0	QS	0/17	0.06	R	23
12	3 yr.	—45	—50	110	Sinus	0.07	0.11	1.8	0.07	3.2	rS	2.5/14	0.03	R	
	6 yr.	—35	—30	95	Sinus	0.07	0.13	0.6	0.07	2.2	rS	3/21	0.04	[illegible]	
14	5 yr.	—20	—20	105	Sinus	0.12	0.13	2.2	0.07	3.0	[illegible]	1/17	0.05	[illegible]	
	8 yr.	+45	+45	190	SVT	—	0.06	—	—	—	[illegible]	1.5/22	0.02	[illegible]	[illegible]
	8 yr.	—50	—20	130	Sinus	0.12	0.13	2.4	0.09	2.0	rS	2/10	0.0[illegible]	[illegible]	
18	13 yr.	—50	—50	75	Sinus	0.12	0.18	1.0	0.10	—	[illegible]	1.5/12	[illegible]	[illegible]	12
	13 yr.	—50	—50	160	SVT	—	0.19	—	—	—	[illegible]	1.[illegible]	[illegible]	[illegible] s'r''s''	
	20 yr.	—110	—105	80	Sinus	0.12	0.16	1.3	0.12	2.5	Rs	[illegible]	[illegible]	Rs	25/[illegible]
Y/S*	20 yr.	—40	—50	70	Sinus	0.14	0.20	2.0	0.10	—	—	—	—	—	—

*Case of Yater and Shapiro.[1]

the original tracing in this case, reportedly the first electrocardiogram published in this anomaly, and agree with his interpretation.

Two general groups of W-P-W pattern have been described, those with right axis (called type A by Sodi-Pallares[41]), and those with left axis (type B). The left axis in these cases was present by both voltage and area analysis. In type B the complexes simulate left bundle-branch block—with QS complexes usually present in leads II, III, and aV_F, and upright ventricular complexes in the left precordial leads.

In 5 of our 6 cases, the W-P-W pattern was present on all occasions (all patients having at least 2 tracings), while in 1 (case 6) this pattern was seen only once. On other occasions there was a prolonged P-R interval and right bundle-branch block (fig. 3).

Sodi-Pallares[41] reported 3 cases of Ebstein's anomaly with type B W-P-W patterns. Single cases of W-P-W patterns in this anomaly have been published by Lev et al.,[23] Gøtzsche and Falholt,[16] Gotshalk et al.,[20] Vogt,[11] Hetjmancik and Herrmann,[43] Hernandez et al.,[15] and Mahaim and van Nieuwenhuizen.[26] The cases reported by Bruce, Yu, et al.[44, 45] and Yim and Yu[46] also appear to fall into this group. In several of these cases the electrocardiogram showed normal rather than left axis, and Vogt's[11] case alternated her W-P-W pattern with a nodal rhythm on occasion. Kezdi and Wennemark[34] have recorded a transient W-P-W pattern during the catheterization of the right ventricle in a patient with Ebstein's defect.

The combination of type B W-P-W pattern and cyanotic congenital heart disease was considered to be diagnostic of Ebstein's anomaly by Sodi-Pallares.[41] However, Hetjmancik and Herrmann[43] recently described a case of transposition of the great vessels with W-P-W pattern. We have also seen an exceptional case of this type in which postmortem study showed complete transposition of the great vessels with patent foramen ovale. However, this electrocardiogram showed a normal axis.

On the other hand, the occurrence of type B W-P-W in a patient with cyanotic congenital heart disease and normal to decreased pulmonary vascular markings appears to be highly suggestive of Ebstein's anomaly. Four of our 6 cases and that of Yater and Shapiro[1] fall into this category. The other 2 remain acyanotic at ages 4 and 7, but may be expected to become cyanotic in the future. That this combination is not diagnostic is shown by Keith's[47] mention of a case of tricuspid atresia with the W-P-W pattern, and the postmortem study by de Oliveira et al.[48] of a case

of tetralogy of Fallot with a variant of the type B pattern.

Three patients (6, 14, 18) of the 6 with W-P-W gave a history of recurrent attacks of tachycardia; in contrast, only 4 of the other 17 cases gave a similar history.

Tall peaked P waves ("P pulmonale") occurred in the right precordial leads in 5 of the 6 cases. There again appears to be a correlation between the height of the P wave and the clinical symptomatology; the tallest waves occurred in the 2 deceased patients, and the only normal P waves occurred in the lone asymptomatic patient (case 10) in this group. The P wave was always positive in leads I, II, aV_L, aV_F, and V_2 to V_6, always negative in aV_R, and variable in the other leads.

All 6 cases showed type B W-P-W pattern, with tall R waves in lead I and deep S waves in lead III—up to 27 mm. The right precordial leads showed rS patterns with a depth up to 22 mm. There was decreasing height of RS as increasing notching and slurring appeared with age. In the left precordial leads there was usually a high R wave, up to 34 mm. In the presence of type B W-P-W these observations cannot be interpreted as left ventricular hypertrophy or "strain."

Significantly, there were no normal tracings among the 70 or more electrocardiograms taken of our 23 patients.

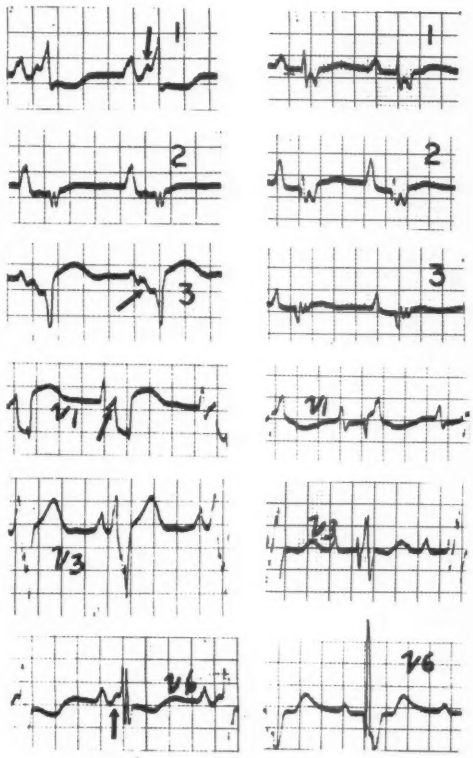


FIG. 3. Electrocardiograms of case 6. *Left.* 3/24/55 W-P-W pattern (type B) with normal P-R interval (0.14) in lead I. *Arrows* indicate "delta" waves. *Right.* 12/15/55. Note the right bundle-branch block without W-P-W pattern but with prolonged P-R interval (0.24) in lead I.

PHONOCARDIOGRAPHY

Phonocardiograms were recorded in 12 of our 23 patients. In all cases the first sound was delayed (0.05 second or greater) after the onset of the QRS complex on the simultaneous electrocardiogram, as compared with the normal value of 0.02 to 0.04 second. The first sound was of normal intensity, though the second component of this sound was invariably louder than the first component, and was maximal at the apex or the lower left sternal border. It was not possible to measure the duration of the first sound inasmuch as the first sound regularly blended in with the succeeding medium frequency (100 to 600 cycles) systolic murmur. This murmur varied from a short decrescendo murmur in early and mid-systole in 8 cases to a descrescendo or crescendo-decrescendo pansystolic murmur in the other 4 cases. The murmurs varied in intensity from very soft to very loud, and were maximal at the apex or lower left sternal border.

The second sound was of normal intensity in 8 cases. In 2 cases it was completely obscured by murmurs. In 1 case (10) it was of less intensity than usual, and in the other (12) the sound was of greater intensity and was the only instance in which "splitting" was noted. Except for this latter case, all showed a second sound of normal duration. The second sound was usually maximal in intensity in the pulmonic area, but in some cases

was loudest along the lower left sternal border or at the apex.

A discrete third heart sound or short mid-diastolic murmur was noted in 9 cases, usually best observed at the lower left sternal border. In another case (7) the area usually occupied by the third heart sound was filled by an early diastolic murmur. In the other 2 patients, both young children, neither a third heart sound nor a diastolic murmur was present. The third heart sound or mid-diastolic murmur was regularly of low frequency (90 to 150 cycles).

A presystolic extra sound was noted in 2 cases, and a presystolic murmur of varying type was present in 4 others. In the 1 case, in which we have serial phonocardiograms (case 18), there was a change from a presystolic extra sound to a definite presystolic murmur over a period of 6 years. In the other 5 cases, all children who are completely or relatively asymptomatic, no presystolic sound or murmur was present. This murmur or sound was regularly of medium frequency and maximal at the lower left sternal border or apex. A continuous systolic-diastolic vibration was noted in 3 cases (4, 6, 7), all of whom showed fibrinous pericarditis at postmortem examination.

In general our findings resemble those of Mayer, Nadas, and Ongley.[14] They found the first sound to be delayed, of normal intensity, and maximal at the apex. The second sound was maximal at the left sternal border or apex in their 5 patients. The systolic murmur was described by them as being of moderate intensity, of medium frequency, and of decrescendo or crescendo-decrescendo configuration. A presystolic murmur of medium frequency and intensity was uniformly noted as well as a low-frequency mid-diastolic murmur at the left sternal border or apex in 2 cases.

Diminution or absence of the first heart sound noted by Vacca et al.[49] was not seen on our phonocardiograms. Nor are our findings in agreement with those of Voill and Sterz,[50] who labeled the second portion of the first sound as "4'" to conform with Michel's[42] theory that delayed polarization of the atrialized ventricle manifests itself as a separate late deflection in the QRS complex (and termed P' because of its resemblance to the original P wave).

Cardiac Catheterization (Table 5)

Seventeen of our 23 patients with Ebstein's anomaly have undergone cardiac catheterization, several having had more than 1 study. There have been no deaths attributable to this procedure and no serious complications. Two pediatric cases (5, 14) developed bouts of supraventricular tachycardia during catheterization, but these were readily controlled by ocular pressure or digitalization.

Several authors[9, 12, 14, 18, 51] have reported fatalities with this procedure, and the general impression has developed that this procedure is contraindicated or unwise in patients with this defect. Our catheterization studies were done under local anesthesia. Whether this technic or chance accounts for our lack of mortality is difficult to decide. Although we recognize that patients with this malformation undoubtedly represent a higher risk, we still think that cardiac catheterization is indicated if the diagnosis cannot definitely be established by other means.

In 6 patients the pulmonary artery was not entered. However, the primary purpose of catheterization was considered to be the establishment of a normal or slightly elevated right ventricular pressure and the documentation of the location of the tricuspid valve. Generally, the tricuspid valve was found to be 2 to 4 cm. to the left of the spine in the anteroposterior view. In 3 cases, the valve was located over the spine, but "lower and more anterior" than usual. This has also been noted by Mayer et al.[14] and Kilby et al.[13] Evidence of an enlarged right atrium was found consistently. In the cases in which the pulmonary artery was entered, the pulmonic valve was normally located. We have had no experience with the use of an intracavitary electrode at catheterization. This has been found to be of value by Sodi-Pallares,[41] Hernandez et al.,[15] and Yim and Yu.[46]

TABLE 5.—*Cardiac Catheterization Data*

Case no.	Age (yr.)	Pressure in mm. Hg Systolic/early diastolic/late diastolic (mean) PA	RV	RA	Oxygen content in volumes per 100 ml. (Van Slyke) Capacity	PA	RV	RA	SVC	IVC	Systemic Artery
4	8*	22/10	22/6	(6)	—	—	—	—	—	—	—
	10†	—	—	—	—	—	—	—	—	—	—
5	9	—	16/-5	11/0	20.6	—	—	12.6	9.4	—	—
6	6‡	(26.5)	29/0	—	19.5	12.9	13.0	13.0	12.9	—	17.3 (88.5%)
	10§	22/6	22/1	21/5	—	58%	57%	55%	—	44%	(87.0%)
8	14	20/10 (12)	40/2/8	8/0 (2.5)	20.3	15.7	—	15.6	16.3	14.3	19.5 (94.3%)
9	2	11/4.5	15/-1/3	3.5/2.5	16.75	12.0	12.3	12.4	12.5	—	16.3 (95.5%)
10	4	27.5/15 (22.5)	27.5/1/4	8/1 (5)	17.6	12.8	13.2	12.0	11.3	11.9	17.6 (98.3%)
11	4	19/10	21/0/2	10/5 (7)	18.9	13.1	12.6	11.0	11.1	—	18.5 (96.1%)
12	7	—	11/6	8/3 (5)	17.7	—	13.3	12.6	12.9	13.5	17.5 (96.7%)
13	8	29/12 (15)	30/2/7	10/7	18.8	13.8	13.6	13.1	13.8	14.6	18.3 (95.9%)
14	8	23/13 (16)	26/4/10	16/0 (14)	22.4	14.8	12.3	13.2	13.0	—	18.7¶ (82.0%)
15	9	—	24/-5/10	9/6 (8)	17.0	—	12.0	11.9	11.7	13.0	17.0 (98.3%)
16	8	19/6	25/0/4	7/4	17.8	11.1	11.0	10.7	10.4	—	17.5 (97.2%)
17	10	—	15/0/3	9/0	19.0	—	13.0	13.1	13.0	—	18.2 (94.2%)
19	15	—	24/-1/2	8/4	29.7	—	22.9	22.8	17.7	—	—
	20	18/9 (12)	18/0/6	13/3	26.1	21.1	—	—	16.7	—	22.2 (83.7%)
20	28	—	19/0/7	10/0 (5)	27.9	—	18.4	16.8	14.7	16.0	20.5 (72.4%)
21	35	13.5/3 (8)	14/0/8	13.5/0 (3)	21.0	16.0	16.4	16.1	13.4	—	20.2 (94.6%)
23	35	19/3	20/0/3	10/-3 (2)	15.5	11.9	11.8	11.8	11.0	—	15.7 (99.2%)

*Catheterization at Columbia-Presbyterian Medical Center, New York, N. Y.

†Catheterization by Dr. Alfred R. Henderson, Asbury Park, N. J. No data available.

‡Catheterization by Dr. James Campbell, Chairman, Department of Medicine, Presbyterian Hospital, Chicago, Ill.

§Catheterization at Walter Reed Army Medical Center, Washington, D. C.

¶Left ventricular sample.

The pulmonary artery pressure varied between 14 and 29 mm. Hg systolic to 3 to 15 mm. Hg diastolic. Infrequently, the pulmonary artery pressure tracing resembled the right atrial or right ventricular tracing, an observation reported by several authors.[9, 27] In addition, the pulmonary artery pressure tracing often showed a small initial wave occurring after the P wave on the simultaneously recorded electrocardiogram. Blacket et al.[9] and Blount et al.[7] found similar tracings, and postulated that this early deflection represented initial pulmonary bed perfusion by the right atrium. Taken as a group, the pulmonary artery tracings on our patients showed great variation in contour.

Right ventricular pressures ranged from 11 to 40 mm. Hg systolic and −5 to 10 mm. Hg diastolic. In 4 of the 14 cases in which right ventricular end-diastolic pressure was recorded, the value was above 7 mm. Hg. Only 1 of our cases (8) had a right ventricular pressure above 30 mm. Hg, this individual having a systolic pressure of 40 mm. and a diastolic of −2 to 8 mm. Hg. This patient had a differential of 20 mm. Hg across the pulmonic valve, though at postmortem examination there was no evidence of anatomic stenosis. A similar differential across the pulmonic valve has been recorded by Kezdi and Wennemark.[34] Several other writers[13, 28, 37] have also reported cases with the systolic pressure in the right ventricle above 30 mm. Hg, but none had a differential pressure across the pulmonic valve greater than 12 mm. Hg.

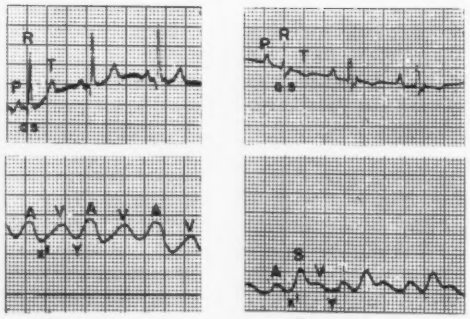


FIG. 4. Simultaneous electrocardiogram and pressure tracing in right atrium during cardiac catheterization in case 5 to demonstrate additional abnormal wave ("s") present in Ebstein's defect.

With 1 exception (case 9), the right atrial pressure was higher than normal, ranging from 7 to 21 mm. Hg systolic and from −2 to 7 mm. Hg diastolic.

Assessment of the physiologic competence of the tricuspid valve from pathologic material is difficult and often unreliable. A review of the pathologic material nevertheless suggested that stenosis was predominant in 2 cases (2, 3) and insufficiency predominant in 6. In 1 of the latter (case 5) there appeared to be evidence also of stenosis.

Physiologic observations tended to agree with postmortem interpretations. If we assume that one of the criteria of tricuspid stenosis is the occurrence of a right atrial diastolic pressure higher than the right ventricular end-diastolic pressure, then 4 of the catheterized patients had elements of stenosis.

Again, if we assume that the presence of an "s" wave (fig. 4) in the right atrial tracing may be considered a sign of tricuspid incompetence,[52-54] then at least 10 of our patients would have a degree of tricuspid insufficiency. The "s" wave follows the QRS complex on the simultaneously recorded electrocardiogram and decreases the X′ descent in the normal atrial pattern. Shephard[52] has described the occurrence of this wave in 3 cases of Ebstein's anomaly as well as in adults with severe pulmonary valvular stenosis. Korner and Shillingford[55] have noted the "s" wave in congestive heart failure, and we have noted it on occasion in cases of complete ostium primum.

In 14 of our cases, the right atrial tracing was suitable for interpretation, and all of these showed definite "s" waves. The height of the "s" wave varied from small 2 mm. deflections to waves large enough partially to obliterate the X′ descent and the V wave of the normal atrial pattern. In 4 cases, the A wave was the most prominent, and in the previously mentioned 10 cases the "s" wave was the larger.

Thus, the 4 patients with physiologic stenosis (5, 6, 11, 19) were also found to have concomitant evidence of physiologic incompetence. Six patients would then appear to show physiologic insufficiency alone, while the other 4 showed reasonably normal tricuspid function under the conditions of the study. It would seem logical that progressive cardiac enlargement, with the concomitant dilatation of the false tricuspid annulus, would enhance the development of valvular insufficiency. Ebstein's defect thus presents a continuum of tricuspid function, from anatomic and physiologic stenosis to insufficiency, some cases having elements of both and other patients approaching normal.

In those catheterizations in which sufficient data were available for the calculation of physiologic values, 4 studies showed systemic arterial desaturation, and the 11 others were fully saturated (94 per cent or greater).

In the desaturated group, the average systemic saturation was 81.5 per cent. The average pulmonary blood flow was 2.5 L./M.^{2}/min., and the average systemic blood flow 3.0 L./M.^{2}/min.—indicating a small net right-to-left shunt. However, the actual calculated average right-to-left shunt was about 1 L./M.^{2}/min., balanced in 3 patients by a simultaneous average left-to-right shunt of about 0.6 L./M.^{2}/min.—both presumably at the atrial level. Thus, in our desaturated group, both the average systemic and pulmonary blood flow would appear to be less than the normal average of 4.0 L./M.^{2}/min. As a consequence, the average total calculated pulmonary resist-

ance in dynes/cm./sec.[5] was 2.2 times greater than normal for the surface area of these patients.

In the 11 patients who were fully saturated, the average saturation was 96.5 per cent. In contrast to the other group, the pulmonary and systemic flows approach normal, being about 3.5 L./M.^{2}/min. The average total calculated pulmonary resistance in this group is normal. One patient (21) would appear to have a left-to-right shunt at the atrial level.

Whether or not these physiologic differences are significant or represent errors inherent in sampling or calculations cannot be stated at the present time.

Differential Diagnosis

The following is limited to those clinical entities having normal or decreased pulmonary vasculature by roentgenograms.

1. Pulmonic Valvular Stenosis, with or without Atrial Septal Defect

The young child with these malformations, particularly if in cardiac failure, may have a cardiac contour similar to some seen in Ebstein's defect. Diminished pulmonary vasculature and peaked P waves may also be seen in both anomalies. However, the harsh murmur of pulmonic stenosis in the primary pulmonary area (with the absence of a diastolic murmur), the systolic thrill in the same area and often in the suprasternal notch, and the marked right ventricular hypertrophy on the electrocardiogram help to identify this defect.

2. Myocarditis, Endocardial Fibroelastosis, and Familial Cardiomegaly

The cardiac contour, cardiomegaly with weak pulsations, distant heart sounds, increase in the P-R interval, diffuse ST segment and T wave changes, and the W-P-W pattern may be seen in these conditions and in Ebstein's anomaly.

In differentiating these lesions, left atrial enlargement on the roentgenogram should be of definite value, since it is often present in the above entities, and has not been seen in any of our series of Ebstein's anomaly. In addition, the pulmonary vascular markings are normal or even "full" in these diseases, even in the presence of a markedly enlarged heart; in contrast, in Ebstein's malformation, the very large heart is usually accompanied by decreased pulmonary vascular markings. Negative T waves in the left precordial leads would suggest endocardial fibroelastosis in the child, particularly if associated with cardiomegaly. The history may be of some aid in pointing to specific etiologic factors in myocarditis.

3. Tricuspid Atresia

Similarities between this malformation and Ebstein's anomaly include cardiac contour, peaked P waves, decreased pulmonary vasculature, cyanosis, and the electrocardiogram when the Ebstein's patient has a type B W-P-W pattern. This latter pattern would have left axis deviation, small or absent R waves in the right precordial leads, and tall R waves in the left precordial leads.

However, individuals with tricuspid atresia usually have left atrial enlargement, and ordinarily show a greater degree of cyanosis at an earlier age. The children with this malformation are usually dyspneic at rest, and show growth retardation.

4. Tetralogy of Fallot

This malformation may be confused with Ebstein's anomaly because cyanosis, decreased pulmonary vasculature, similar cardiac contour (when the Ebstein's has a normal or only slightly enlarged heart), syncope, squatting, peaked P waves, and right axis deviation may be found in individuals with either of these defects. Historically, those individuals with Ebstein's anomaly subjected to an extracardiac shunt procedure were diagnosed, as tetralogy of Fallot, trilogy of Fallot, or tricuspid atresia.[22, 23, 25, 31, 59]

The cyanotic tetralogy, however, invariably has marked right ventricular hypertrophy with little delay in intraventricular conduction. The squatting and syncopal episodes are usually more frequent and severe, diastolic murmurs are rarely heard, and loud systolic murmurs are heard from the primary pulmonary area down the left sternal border.

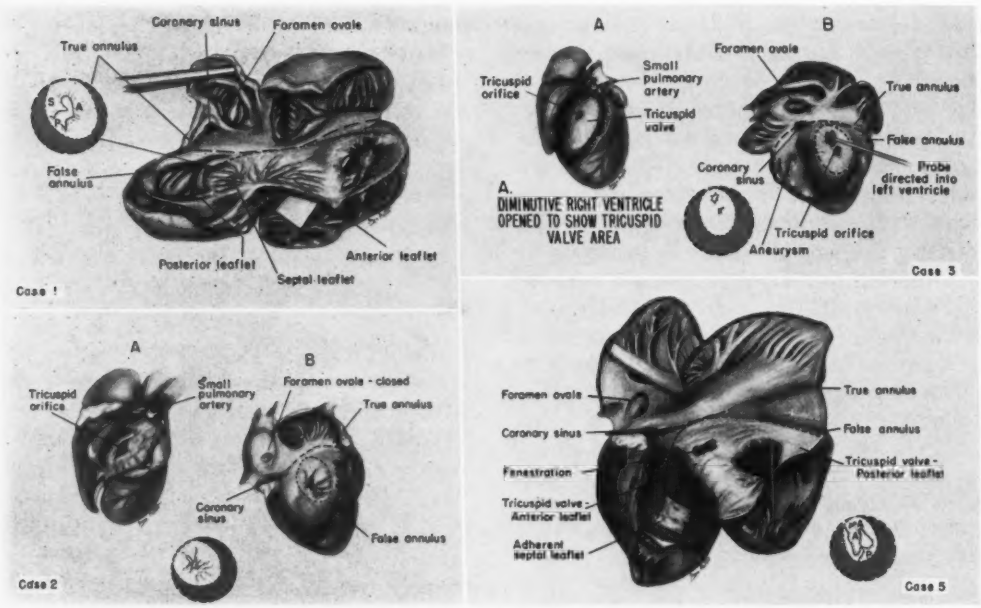


FIG. 5 *Top left.* Drawings of autopsy specimen of case 1. Note separate diagram of tricuspid valve area as viewed from above. *(Courtesy of Dr. Frederick H. Lott, Northwestern Hospital, Minneapolis, Minn.)*

FIG. 6 *Bottom left.* Drawings of autopsy specimen of case 2. The small tricuspid orifice should be noted. *A.* Diminutive right ventricle opened to show tricuspid valve area. *B.* Right atrium and atrialized ventricle opened to show relationships. *(Courtesy of Dr. Kano Ikeda, Children's Hospital, St. Paul, Minn.)*

FIG. 7 *top right.* Drawings of autopsy specimen of case 3. The salient features are that the ventricular septal defect communicates directly from the left ventricle to "atrialized" portion of the right ventricle and that the tricuspid orifice is very small. *A.* Diminutive right ventricle opened to show tricuspid valve area. *B.* Right atrium and atrialized ventricle opened to show relationships.

FIG. 8 *Bottom right.* Drawing of autopsy specimen of case 5. *(Courtesy of Dr. E. S. Olson, St. Luke's Hospital, Racine, Wis.)*

5. Rheumatic Heart Disease

On rare occasions, in the older child or adult, the cardiac contour, the electrocardiogram, and the murmurs may be similar in Ebstein's anomaly and in rheumatic heart disease. This would be particularly so when the rheumatic lesion involves the tricuspid valve. This occurred in 1 of our adult cases who was diagnosed as having Ebstein's malformation because of "typical" clinical and catheterization findings. However, postmortem study showed a huge right atrium secondary to severe tricuspid stenosis. In addition, this case had calcific mitral and aortic stenosis. Of course, these entities can occur concomitantly, as happened in the unfortunate young man reported by Nöcker and Uibe.[56]

Again, the presence of left atrial enlargement would suggest rheumatic heart disease. A history of acute inflammatory disease would be helpful, and the presence of typical mitral or aortic murmurs would aid the clinician.

6. Pericardial Effusion

A large globular cardiac contour, weak cardiac pulsations, distant heart sounds, absence of any murmur, low voltage, and diffuse ST-T changes may be found in both clinical entities.

However, absent or very weak cardiac pul-

sations, pulsus paradoxus on physical examination, and the clinical history on occasion, would suggest that the large cardiac contour is caused by a pericardial effusion.

7. Congenital Tricuspid Insufficiency[57]

The clinical, roentgenographic, and electrocardiographic findings may be very similar, and differentiation would appear to require cardiac catheterization to demonstrate the critical displacement of the tricuspid valve in Ebstein's anomaly.

8. Aortic Stenosis

When the heart is only slightly enlarged, when a parasternal murmur of fair intensity is present, and particularly when type B W-P-W is interpreted as left bundle-branch block or left ventricular hypertrophy, then an Ebstein's anomaly may be erroneously diagnosed as "mild aortic stenosis." Misdiagnosis here is thus one of misinterpretation.

In addition, 1 of our patients was originally diagnosed as a "psychoneurotic" because of the multiplicity of her complaints and the paucity of her physical findings.

In most of the preceding conditions, it would be very unusual to hear a "triple" or quadruple" rhythm. Likewise, most of them would not have the marked right bundle-branch block and low voltages (particularly in the right precordial leads) so often seen in Ebstein's anomaly. The presence of a W-P-W pattern with congenital heart disease also should suggest Ebstein's anomaly, although the authors have infrequently seen this pattern in other congenital lesions.

Surgical Considerations

Prior to the accumulation of clinical knowledge that led to methods of detecting this defect, cases of Ebstein's anomaly were sometimes subjected to shunt procedures.[22, 23, 25, 31, 59] The operation was of no benefit, and the correct diagnosis became evident at postmortem examination.

In the widely quoted case of Wright et al.[27] temporary relief was gained by closing the incompetent foramen ovale. In marked tricuspid insufficiency, however, this palliative procedure would appear to have little usefulness. Three subsequent cases operated upon at the same center died during the induction of anesthesia or in the immediate postoperative period.

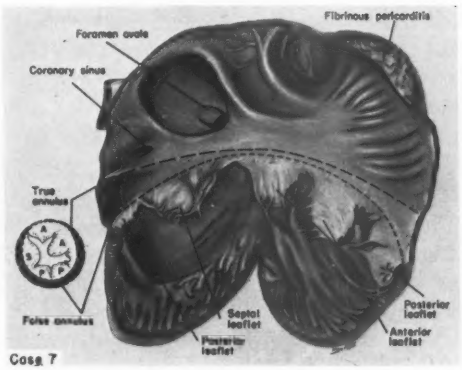


Fig. 9. Drawing of autopsy specimen of case 7. Note relative close proximity of the true and false annulus.

Recently a new surgical procedure for this anomaly was devised at our hospital.[58] During total cardiopulmonary bypass with the helix reservoir pump oxygenator, a right atrial cardiotomy is made. The displaced leaflets are brought up to the true annulus by means of a plicating technic that excludes the thin wall of the atrialized portion of the right ventricle. Fenestrations in the leaflets are closed with silk sutures, and the atrial septal defect is closed. The tricuspid ring is reduced in diameter. The plicating sutures are so placed that they will interrupt the abnormal conduction pathways described by Lev et al.[23] in a case with W-P-W.

This special procedure was attempted in cases 6 and 7, but neither patient survived. The former patient was a semi-invalid because of his disabling paroxysms of tachycardia; the latter patient was in intractable cardiac failure even on a full medical program. Another, case 4, also in severe cardiac failure with thromboembolic manifestations, had cardiac arrest during the induction of anesthesia. Obviously, a trial on better-risk patients will be required before this operation can be evaluated properly.

It is of interest to note that at operation it

was not possible to tell whether the "atrialized ventricle" was contracting with the right atrium or with the "functional" right ventricle.

Pathologic Features

The mode of death in 3 of our cases has been noted. Cases 1, 3, and 5 had severe cardiac failure; case 2 died in cardiac failure shortly after the onset of the nephrotic syndrome; and case 8 died unexpectedly while sitting at his desk in school. Some of the postmortem specimens of the heart (figs. 5 to 9) demonstrate strikingly the typical abnormal positions of the tricuspid valve. The anterior leaflet is usually the largest and best developed leaflet and is attached to the true annulus along its medial aspect. The septal (medial) and posterior leaflets are displaced down from the true annulus, the posterior leaflet usually showing the greatest degree of deformity to the point of being absent entirely.

The valve tissue proper may be thick or thin, intact or with multiple perforations, or smooth or nodular. Leaflets may appear to be entirely functional, or they may be adherent to the endocardium ("tethered down"). The chordae tendineae vary from minute useless structures to those that approach normal. The papillary muscles similarly show wide variation in structure.

The right atrium is consistently enlarged, with dilatation and hypertrophy invariably present. On the other hand, the "atrialized" portion of the ventricle is always very thin, occasionally with thin aneurysmal areas. This latter feature was present in the 2 infants that died (cases 1, 3). The "functional" right ventricle may be rudimentary or very large, and its wall may be thin or hypertrophied or may show areas of each. The infundibulum usually shows hypertrophy. The size of the "functional" right ventricle varies more or less inversely with the "atrialized" right ventricle. Pechstein[59] has attempted to classify this anomaly into 4 separate morphologic groups, utilizing valve positions and proportion of "atrialized" to "functional" right ventricle as the basis of his criteria.

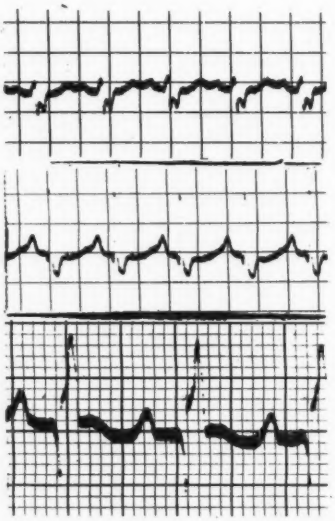


Fig. 10. Electrocardiogram of case 1 taken at 5 hours of age: *Top*, lead I; *middle*, lead II; *bottom*, lead V_1. Note prolonged P-R interval (0.14) for age and rate, complete right bundle-branch block (QRS 0.11), and peaked P waves.

All but 2 of our autopsied cases (2, 8) had an incompetent or fenestrated foramen ovale. Case 1 showed a patent ductus arteriosus, but this was of dubious significance inasmuch as death occurred shortly after birth. Only 1 other case (3), who died at 3½ months, had an associated cardiac abnormality—a ventricular septal defect. Although this was present, there was no evidence of increased pulmonary blood flow. Any blood shunting through this ventricular defect had 2 possible modes of exit: through the minute 3 mm. tricuspid orifice into the right ventricle, or through the foramen ovale to the left atrium. In view of the decreased vascularity on the roentgenograms, it is apparent that the small tricuspid aperture was effective in preventing excessive or even normal pulmonary blood flow.

The pulmonic, aortic, and mitral valves were uniformly normal, except for "slight nodularity" of the mitral valve in case 8. An attached thrombus was present in the apex of the left ventricle in case 5, and a nonattached thrombus practically filled the cavity of the small right ventricle in case 2. Fibrinous pericardi-

tis over the right atrial and right ventricular surfaces was seen in cases 4, 6, and 7.

Although we have seen more than 40 cases of corrected transposition of the great vessels at our hospital in the past 5 years (17 of which have been reported by Anderson et al.[60]), we have recognized no cases with downward displacement of the left-sided atrioventricular valve, so-called "left-sided Ebstein's anomaly."

Other authors[13, 61] have reported the ostium primum syndrome in conjunction with Ebstein's anomaly, and 3 other cases[5, 14, 62] have been described with an interventricular septal defect. In addition, Keith et al.[5] had a case of Ebstein's anomaly with pulmonary atresia and multiple atrial septal defects.

Chronic passive congestion, often with atrophy of the surrounding liver cells to the point of cardiac cirrhosis (case 6), was usually noted in our autopsied cases. One (case 4) showed an area of adenomatous hyperplasia of the liver in addition to large areas of central atrophy.

Four of our 8 cases showed pathologic changes in the brain. Case 2 showed an area of patchy demyelinization in the frontal cortex, in addition to congestion and petechiae. Case 5 had congestion of all the vascular spaces and a large area of cystic degeneration in the floor of the fourth ventricle. Case 4 exhibited congestion of the vessels and areas of recent encephalomalacia in the left inferior parietal lobule and the inferior surface of the right occipital lobe, as well as slight calcification of the basal ganglia. Case 7 had a large cystic area of encephalomalacia and glial formation in the left cerebral hemisphere. The latter 2 patients had clinical evidence of cerebral emboli or thrombi.

Infarcts of the spleen and kidney were seen in case 7 and in the kidney in case 4.

None of the autopsied cases showed evidence of pulmonary tuberculosis, and such evidence is not present in the 15 living patients.

Summary

Twenty-three cases of Ebstein's malformation of the tricuspid valve are reviewed, including 8 with postmortem examinations. This anomaly occurs equally in males and females, and has been estimated to constitute less than 1 per cent of all congenital heart defects.

There was no evident etiologic relationship to various prenatal factors, birth order, maternal age, birth weight, or month of birth. Only 1 patient had a relative with known congenital heart disease.

Twelve of the 23 cases had neonatal symptoms or signs, generally cyanosis or a murmur. This neonatal cyanosis invariably diminished or disappeared with time, but recurred later in life in all cases. Symptoms after the neonatal period included dyspnea, cyanosis, excessive fatigue, central nervous system symptoms, cardiac failure, precordial or epigastric pain, paroxyms of tachycardia, and squatting.

The most common physical findings were a systolic murmur, a second sound which was always heard as well over the pulmonic area as over the aortic area, normal pulmonary breath sounds, cardiomegaly, normal growth features, a "triple" or "quadruple" rhythm, cyanosis, a systolic thrill, a diffuse area of maximal impulse, a diastolic murmur, a "split" first sound, "metallic" or "clicking" heart tones, cardiac failure, and an unusual "facial erythema."

Roentgen studies regularly showed cardiomegaly, normal to decreased pulmonary vasculature, and a normal-sized left atrium. Cardiac size and contour varied widely, though in certain cases the "box-like" configuration was diagnostic.

The most frequent electrocardiographic findings in the 18 patients with a normal sinoatrial rhythm were incomplete or complete right bundle-branch block (often with widely splintered or notched complexes), peaked and occasionally prolonged P waves, low voltage QRS complexes in the right precordial leads (none had an R wave in V_1 exceeding 8 mm. in height), and right axis deviation. Five cases showed a constant type B Wolff-Parkinson-White (W-P-W) pattern, and another did so intermittently. The presence of a type B W-P-W pattern in a cyanotic child with congenital heart disease and normal to decreased

pulmonary vasculature should immediately suggest the possibility of Ebstein's anomaly.

Phonocardiography was performed in 12 patients. This is a valuable adjunct in elucidating the auscultatory findings.

A total of 20 right heart catheterizations were carried out in these 23 patients, without any mortality or serious complications. The principal value of cardiac catheterization is in documenting the location of the tricuspid valve, and in obtaining pressure tracings in the various vessels and chambers.

This defect may be confused with pulmonary valvular stenosis, myocarditis, endocardial fibroelastosis, tetralogy of Fallot, tricuspid atresia, rheumatic heart disease, pericardial effusion, congenital tricuspid insufficiency, and "mild aortic stenosis."

Two of our patients underwent a new type of surgical procedure, but neither survived.

Physiologic data and studies of postmortem specimens indicate that Ebstein's anomaly represents a continuum from predominant tricuspid stenosis to predominant tricuspid insufficiency, with some having elements of both, and others approaching normal.

Acknowledgment

We acknowledge gratefully the many persons who contributed clinical and pathologic data on the cases or aided in the preparation of the manuscript, particularly Robert A. Good, Ph.D., M.D., American Legion Memorial Heart Research Professor of Pediatrics, without whose generous aid and advice this manuscript could not have been completed.

Summario in Interlingua

Es presentate un revista de 23 casos del malformation de Ebstein del valvula tricuspidal. In 8, datos necroptic es includite. Iste anomalia occurre equalmente in masculos e in femininas. Il ha essite estimate que illo constitue minus que 1 pro cento de omne congenite defectos cardiac.

Esseva notate nulle evidente relation etiologic con varie factores prenatal, con le numero del fraternos senior, le etate del matre, le peso natal, o le mense del nascentia. Solmente 1 del patientes habeva un consanguineo con cognoscite morbo cardiac congenite.

Dece-duo del 23 habeva symptomas o signos neonatal, generalmente cyanosis o un murmure. Le cyanosis neonatal se diminueva o dispareva invariabilemente in le curso del tempore, sed in omne casos illo recurreva a un etate plus avantiate. Le symptomas post le periodo neonatal includeva dyspnea, cyanosis, grados excessive de fatiga, symptomas del systema nervose central, disfallimento cardiac, dolores precordial o epigastric, paroxysmos de tachycardia, e statura pycnic.

Le plus commun constatationes physic esseva un murmure systolic, un secunde sono (semper audible supra le area pulmonic e supra le area aortic), normal sonos pulmonorespiratori, cardiomegalia, normal characteristicas de crescentia, un "triple" o "quadruple" rhythmo, cyanosis, un fremito systolic, un area diffuse de impulso maximal, un murmure diastolic, un "findite" prime sono, sonos cardiac "metallic," disfallimento cardiac, e un inusual "erythema facial."

Studios roentgenologic monstrava regularmente cardiomegalia, normal o reducite vasculatura pulmonar, e dimensiones normal del atrio sinistre. Le dimensiones e le contorno del corde variava extensemente, ben que in certe casos le configuration "quadrate" esseva diagnostic.

Le plus frequente constatationes electrocardiographic in le 18 patientes con normal rhythmo sino-atrial esseva bloco incomplete o complete de branca dextere (frequentemente con extense segmentation o indentation del complexos), punctate e a vices prolongate undas P, complexos QRS a basse voltage in le derivationes dextero-precordial (un unda R in V_1 de plus que 8 mm de altor non occurreva in ulle del casos), e deviation dextero-axial. In 5 casos, un configuration del typo B de Wolff-Parkinson-White esseva constante, in un sexte caso illo esseva presente intermittentemente. Le presentia de un configuration del typo B de Wolff-Parkinson-White in un puero cyanotic con congenite morbo cardiac e normal o reducite vasculatura pulmonar deberea suggerer immediatemente le possibilitate de anomalia de Ebstein.

Studios phonocardiographic esseva effectuate in 12 patientes. Isto es un adjuncto de valor in le elucidation del constatationes auscultatori.

Un total de 20 catheterisationes dexterocardiac esseva effectuate in iste 23 patientes. Occurreva nulle morte e nulle serie complicationes in consequentia del catheterismo. Le principal valor de iste technica es que illo pote documentar le location del valvula tricuspide e que illo permitte obtener registrationes del pression in le varie vasos e cameras.

Le defecto sub discussion pote esser confundite con stenosis del valvula pulmonar, myocarditis, fibroelastosis endocardial, tetralogia de Fallot, atresia tricuspidal, rheumatic morbo cardiac, effusion pericardial, congenite insufficientia tricuspidal, e le "forma leve de stenosis aortic."

Duo de nostre patientes esseva operate secundo un nove technica chirurgic. Superviveva ni le un ni le altere.

Datos physiologic e studios de specimens necroptic indica que anomalia de Ebstein representa un continuo ab predominante stenosis tricuspidal a predominante insufficientia tricuspidal. In certe casos, il ha elementos de ambes; altere casos approcha un stato normal.

REFERENCES

1. Yater, W. M., and Shapiro, M. J.: Congenital displacement of the tricuspid valve (Ebstein's disease): Review and report of a case with electrocardiographic abnormalities and detailed histologic study of the conduction system. Ann. Int. Med. **11**: 1043, 1937.
2. Taussig, H. B.: Congenital Malformations of the Heart. New York, The Commonwealth Fund, 1947, p. 514.
3. Ebstein, W.: Über einen sehr seltenen Fall von Insufficienz der Valvula tricuspidalis, bedingt durch eine angeborene hochgradige Missbildung derselben. Arch. Anat. u. Physiol. 238, 1866.
4. Abbott, M. E.: Atlas of Congenital Cardiac Disease. New York, The American Heart Association, 1936, p. 24.
5. Keith, J. D., Rowe, R. D., and Vlad, P.: Heart Disease in Infancy and Childhood. New York, Macmillan, 1958, p. 314.
6. Grob, M., Bettex, M., and Rossi, E.: Zur Diagnose des Morbus Ebstein. Helvet. paediat. acta **7**: 85, 1952.
7. Blount, S. G., McCord, M. C., and Gelb, I. J.: Ebstein's anomaly. Circulation **15**: 210, 1957.
8. Bayer, O., Rippert, R., Wolter, H. H., and Loogen, F.: Klinische und physiologische Befunde beim Ebstein-Syndrom: Bericht über 3 Fälle. Ztschr. Kreislaufforsch. **43**: 98, 1954.
9. Blacket, R. B., Sinclair-Smith, B. C., Palmer, A. J., Halliday, J. H., and Maddox, J. K.: Ebstein's disease: A report of five cases. Australasian Ann. Med. **1**: 26, 1952.
10. Hueck, O.: Eine seltene Tricuspidalismissbildung. Arch. path. Anat. **319**: 247, 1950.
11. Vogt, A.: Maladie d'Ebstein avec syndrome de Wolff-Parkinson-White. Ann. paediat. **187**: 286, 1956.
12. Schaede, A.: Zur Diagnostik des Ebstein-Syndromes. Deutsches Arch. klin. Med. **198**: 619, 1951.
13. Kilby, R. A., DuShane, J. W., Wood, E. H., and Burchell, H. B.: Ebstein's malformation: A clinical and laboratory study. Medicine **35**: 161, 1956.
14. Mayer, F. E., Nadas, A. S., and Ongley, P. A.: Ebstein's anomaly: Presentation of ten cases. Circulation **16**: 1057, 1957.
15. Hernandez, F. A., Rochkind, R., and Cooper, H. R.: The intracavitary electrocardiogram in the diagnosis of Ebstein's anomaly. Am. J. Cardiol. **1**: 181, 1958.
16. Gøtzsche, H., and Falholt, W.: Ebstein's anomaly of the tricuspid valve: A review of the literature and report of 6 new cases. Am. Heart J. **47**: 587, 1954.
17. Reynolds, G.: Ebstein's disease: A case diagnosed clinically. Guy's Hosp. Rep. **99**: 276, 1950.
18. Baker, C., Brinton, W. D., and Channell, G. D.: Ebstein's disease. Guy's Hosp. Rep. **99**: 247, 1950.
19. Broadbent, J. C., Wood, E. H., Burchell, H. B., and Parker, R. L.: Ebstein's malformation of the tricuspid valve: Report of 3 cases. Proc. Staff Meet. Mayo Clin. **28**: 79, 1953.
20. Gotshalk, H. C., Civin, H., and Mills, G.: Electrocardiographic changes and brain abscess with malformed tricuspid valve: Report of a case. J.A.M.A. **155**: 1411, 1954.
21. Soloff, L. A., Stauffer, H. M., and Zatuchni, J.: Ebstein's disease. Report of the first case diagnosed during life. Am. J. M. Sc. **222**: 554, 1951.
22. Engle, M. A., Payne, T. P. B., Bruins, C.,

AND TAUSSIG, H. B.: Ebstein's anomaly of the tricuspid valve. Report of three cases and analysis of clinical syndrome. Circulation **1**: 1246, 1950.

23. LEV, M., GIBSON, S., AND MILLER, R. A.: Ebstein's disease with Wolff-Parkinson-White syndrome: Report of a case with histopathologic study of possible conduction pathways. Am. Heart J. **49**: 724, 1955.
24. ZAK, F. G., SUM, P., AND LAROSA, G. A.: Ebstein's disease: Case report. New York State J. Med. **55**: 2519, 1955.
25. GASUL, B. M., WEISS, H., FELL, E. H., DILLON, R. F., FISHER, D. L., AND MARIENFELD, C. J.: Angiocardiography in congenital heart disease correlated with clinical and autopsy findings. Am. J. Dis. Child. **85**: 404, 1953.
26. MAHAIM, C., AND VAN NIEUWENHUIZEN, C. L. C.: Le diagnostic de la maladie d'Ebstein: Cinq nouvelles observations. Arch. mal. coeur **50**: 465, 1957.
27. WRIGHT, J. L., BURCHELL, H. B., KIRKLIN, J. W., AND WOOD, E. H.: Congenital displacement of the tricuspid valve (Ebstein's malformation): Report of a case with closure of an associated foramen ovale for correction of the right-to-left shunt. Proc. Staff Meet., Mayo Clin. **29**: 278, 1954.
28. KERWIN, A. J.: Ebstein's anomaly: Report of a case diagnosed during life. Brit. Heart J. **17**: 109, 1955.
29. MEDD, W. E., MATTHEWS, M. B., AND THURSFIELD, W. R. R.: Ebstein's disease. Thorax **9**: 14, 1954.
30. BAUER, D. DEF.: Ebstein type of tricuspid insufficiency: Roentgen studies in a case with sudden death at the age of 27. Am. J. Roentgenol. **54**: 136, 1945.
31. GOODWIN, J. F., WYNN, A., AND STEINER, R. E.: Ebstein's anomaly of the tricuspid valve. Am. Heart J. **45**: 144, 1953.
32. QUINTIN, P., AND DULUC, J.: Epreuves fonctionnelles cliniques dans un cas de maladie d'Ebstein. Arch. mal. coeur **49**: 346, 1956.
33. GRAUX, P., AND MERLEN, J. F.: Apropos d'un cas de maladie d'Ebstein. Arch. mal. coeur **44**: 263, 1951.
34. KEZDI, P., AND WENNEMARK, J.: Ebstein's malformation: Clinical findings and hemodynamic alterations. Am. J. Cardiol. **2**: 200, 1958.
35. TOURNIAIRE, A., DEYRIEUX, F., AND TARTULIER, M.: Maladie d'Ebstein: Essai de diagnostic clinique. Arch. mal. coeur **42**: 1211, 1949.
36. AMPLATZ, K., LESTER, R. G., SCHIEBLER, G. L., ADAMS, P., JR., AND ANDERSON, R. C.: Roentgen features of Ebstein's anomaly of the tricuspid valve. Am. J. Roentgenol. In press.
37. KJELLBERG, S. R., MANNHEIMER, E., RUDHE, U., AND JONSSON, B.: Diagnosis of Congenital Heart Disease. Chicago, Year Book Publishers, 1955, p. 518.
38. ZIEGLER, R. F.: Electrocardiographic Studies in Normal Infants and Children. Springfield, Ill., Charles C Thomas, 1951, p. 128.
39. VAN LINGEN, B., AND BAUERSFELD, S. R.: The electrocardiogram in Ebstein's anomaly of the tricuspid valve. Am. Heart J. **50**: 13, 1955.
40. BROWN, J. W., HEATH, D., AND WHITAKER, W.: Ebstein's disease. Am. J. Med. **20**: 322, 1956.
41. SODI-PALLARES, D.: New Bases of Electrocardiography. St. Louis, C. V. Mosby, 1956, p. 270.
42. MICHEL, D., GRUNER, G., AND HERBST, M.: Zum elektrokardiographischen Bild des Ebstein-Syndroms. Ztschr. Kreislaufforsch. **44**: 522, 1955.
43. HEJTMANCIK, M. R., AND HERRMANN, G. R.: The electrocardiographic syndrome of short P-R interval and broad QRS complexes: A clinical study of 80 cases. Am. Heart J. **54**: 708, 1957.
44. BRUCE, R. A., YU, P. N. G., LOVEJOY, F. W., JR., MCDOWELL, M. E., AND PEARSON, R.: Ventricular tachycardia during cardiac catheterization of patient with Wolff-Parkinson-White syndrome: Report of a case showing effects of atropine sulfate. Circulation **2**: 245, 1950.
45. YU, P. N. G.: Personal communication.
46. YIM, B. J. B., AND YU, P. N.: Value of an electrode catheter in diagnosis of Ebstein's disease. Circulation **17**: 543, 1958.
47. KEITH, J. D., ROWE, R. D., AND VLAD, P.: Heart Disease in Infancy and Childhood. New York, Macmillan, 1958, p. 451.
48. DE OLIVEIRA, J. M., MENDELSOHN, D., NOGUEIRA, C., AND ZIMMERMAN, H. A.: Wolff-Parkinson-White syndrome and tetralogy of Fallot: Report of a case. Am. J. Cardiol. **2**: 111, 1958.
49. VACCA, J. B., BUSSMANN, D. W., AND MUDD, J. G.: Ebstein's anomaly: Complete review of 108 cases. Am. J. Cardiol. **2**: 210, 1958.
50. VOILL, F., AND STERZ, H.: Zum phonokardiographischen Bild des Ebstein-Syndroms. Ztschr. Kreislaufforsch. **45**: 526, 1956.
51. CAMPBELL, M.: Editorial note. Brit. Heart J. **15**: 363, 1953.
52. SHEPHARD, R. J.: The atrial pressure tracing in congenital heart disease. Brit. Heart J. **17**: 225, 1955.

53. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. J. Clin. Invest. **25**: 639, 1946.

54. Müller, O., and Shillingford, J.: Tricuspid incompetence. Brit. Heart J. **16**: 195, 1954.

55. Korner, P., and Shillingford, J.: The right atrial pulse in congestive heart failure. Brit. Heart J. **16**: 447, 1954.

56. Nöcker, J., and Uibe, P.: Ungewöhnliche Semiotik bei angeborener Trikuspidalanomalie (Ebensteinsches Syndrom). München. med. Wchnschr. **95**: 650, 1953.

57. Barritt, D. W., and Urich, H.: Congenital tricuspid incompetence. Brit. Heart J. **18**: 133, 1956.

58. Hunter, S. W., and Lillehei, C. W.: Ebstein's malformation of the tricuspid valve: Study of a case together with suggestion of a new form of surgical therapy. Dis. Chest **33**: 297, 1958.

59. Pechstein, J.: Beitrag zur Ebsteinschen Anomalie der Valvula tricuspidalis. Arch. Kreislaufforsch. **26**: 282, 1957.

60. Anderson, R. C., Lillehei, C. W., and Lester, R. G.: Corrected transposition of the great vessels of the heart: A review of 17 cases. Pediatrics **20**: 626, 1957.

61. Heigel, A.: Uber eine besondere Form von Entwicklungsstörung der Trikuspidalklappe. Arch. path. Anat. **214**: 301, 1913.

62. Edwards, J. E.: Pathologic features of Ebstein's malformation of the tricuspid valve. Proc. Staff Meet. Mayo Clin. **28**: 89, 1953.

THE MODESTY OF A GREAT MIND

David Brewster

Scottish physicist, 1781-1868

The modesty of Sir Isaac Newton, in reference to his great discoveries, was not founded on any indifference to the fame which they conferred, or upon any erroneous judgment of their importance to science. The whole of his life proves, that he knew his place as a philosopher, and was determined to assert and vindicate his rights. His modesty arose from the depth and extent of his knowledge, which showed him what a small portion of nature he had been able to examine, and how much remained to be explored in the same field in which he had himself labored. In the magnitude of the comparison he recognized his own littleness; and a short time before his death he uttered this memorable sentiment: "I do not know what I may appear to the world, but to myself I seem to have been only like a boy playing on the seashore, and diverting myself in now and then finding a smoother pebble or a prettier shell than ordinary, whilst the great ocean of truth lay all undiscovered before me."—*Memoirs of Sir Isaac Newton.* From *Great Companions. Readings on the Meaning and Conduct of Life from Ancient and Modern Sources.* Vol. II, Boston, The Beacon Press, 1953.

Atrial Flutter as a Manifestation of Digitalis Toxicity

By JAY D. COFFMAN, M.D., AND GERALD H. WHIPPLE, M.D.

Although digitalis overdosage is known to produce a variety of atrial, junctional, and ventricular arrhythmias, atrial flutter due to digitalis intoxication has been rarely reported. The present paper reviews the literature and reports what appears to be the sixteenth case. The available information on the accepted cases of atrial flutter due to digitalis toxicity has been analyzed for clues as to when digitalis can be considered the cause of the flutter.

DIGITALIS is usually administered in the treatment of atrial flutter, but in the exceptional patient it may cause the arrhythmia, and more of the drug could lead to disastrous results. This paper emphasizes the rarity of atrial flutter due to digitalis intoxication, presents criteria to help determine whether digitalis is the cause of a given episode of atrial flutter, and adds what appears to be the sixteenth case to the literature.

CASE REPORT

A 79-year-old man had congestive heart failure for 19 months due to arteriosclerotic heart disease. An electrocardiogram at the onset of his symptoms revealed sinus rhythm at a rate of 106 with a P-R interval of 0.19 second, low QRS voltage, and ST-T abnormalities. He was digitalized and maintained on 0.2 Gm. of digitalis leaf per day and intermittent diuretic therapy. Four weeks prior to admission, following a "cold," all symptoms of congestive failure increased and he was hospitalized.

Physical examination revealed a disoriented man with Cheyne-Stokes respiration. Funduscopic examination showed narrowed, tortuous arterioles with arteriovenous nicking. There was distention of the neck veins. Coarse, moist rales were heard over both lower lung fields posteriorly. The heart was moderately enlarged to percussion. The cardiac rhythm was regular with occasional premature beats; the aortic component of the basal second sound was louder than the pulmonic; a grade III, coarse, blowing systolic murmur was best heard at the apex and was transmitted to the axilla. The liver was enlarged but nontender. There was 1+ pretibial pitting edema. The blood pressure was 152/80.

From the Robert Dawson Evans Memorial Department of Clinical Research and Preventive Medicine, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

The urine showed 1+ protein and rare hyaline and granular casts. The hematocrit level was 46 per cent and the corrected sedimentation rate (Wintrobe) was 32 mm. per hour, the white blood cell count was 12,700. The blood urea nitrogen was 21 mg., the creatinine 1.5 mg., the total protein 7.1 Gm., the albumin 3.4 Gm., and the globulin 3.7 Gm. per 100 ml. The serum sodium was 137 mEq., the potassium 5.9 mEq., the chloride 95 mEq. and the carbon dioxide 27.3 mEq. per liter.

An electrocardiogram showed sinus rhythm at a rate of 110 with a P-R interval of 0.22 second, occasional ventricular premature beats, low QRS voltage, and ST-T abnormalities. A chest film revealed the heart to be generally enlarged, with a cardiothoracic transverse diameter ratio of 17:30, an elongated tortuous calcific aorta, and congested lung fields.

The patient was given two 0.2-mg. doses of lanatoside C intravenously over a 2-hour period. This caused a slight increase in rate and in the number of ventricular premature beats. Consequently, no further digitalis was given for 3 days. Treatment consisted of bed rest, aminophylline suppositories, and a low-sodium diet. No diuretics were given. The patient's disorientation and Cheyne-Stokes respiration became worse. The urine output remained low (about 500 ml. per day) while the blood urea nitrogen rose gradually.

Because of persistent tachycardia and heart failure, digoxin was begun on the fourth hospital day; table 1 shows the dosage of digoxin each day. By the sixth hospital day the patient was much improved. He had lost 4 pounds, was able to lie flat without dyspnea, and his ankle edema had disappeared. However, Cheyne-Stokes respiration and disorientation continued. An electrocardiogram at this time showed a sinus rhythm at a rate of 118 with a P-R interval of 0.22 second and disappearance of the ventricular premature beats. On the twelfth hospital day, after a total of 7.25 mg. of digoxin in 9 days and a weight loss of 10 pounds, the heart rate suddenly slowed. The electrocardiogram (fig. 1) revealed atrial flutter with an atrial rate of 240, an average ventricular rate of 80, and a shifting atrioventricular block.

Ventricular premature beats had reappeared, sometimes in runs of 2. No gastrointestinal symptoms were present. Digoxin was stopped.

The following day the serum potassium was 4.9 mEq. per liter. An electrocardiogram on the fourteenth hospital day showed coarse atrial fibrillation with a ventricular rate of 85; ventricular premature beats had disappeared. The next day an electrocardiogram disclosed reversion to sinus rhythm at a rate of 100 with a P-R interval of 0.24 second. Digitalis was resumed 2 days later without further atrial arrhythmia.

During this period, the patient continued to be disoriented. Despite a marked improvement in the signs of congestive failure, Cheyne-Stokes respiration was still present. Dehydration and a urinary tract infection were treated but he gradually lapsed into coma and died quietly on the twenty-fifth hospital day.

At autopsy, the heart weighed 850 Gm. with marked hypertrophy and dilatation of the left and right ventricles and dilatation of the left atrium. All valves had thin pliable cusps. The chordae tendineae were thin and delicate. There was marked calcification of the left coronary artery, but no occlusion. Extensive patchy fibrosis of the myocardium of the left ventricle was seen microscopically. The lungs showed bronchopneumonia and moderate congestion. The liver was also congested. The kidneys revealed arterial and arteriolar nephrosclerosis. The remainder of the examination, including that of the brain, was noncontributory.

TABLE 1.—*Digitalis Dosage, Cardiac Rhythm, and Serum Potassium Levels during Hospitalization*

Hospital day	Digitalis preparation	Digitalis dosage	Cardiac rhythm	Serum potassium (mEq./L.)
1st	Lanatoside C	0.4 mg.	Normal sinus rhythm	5.9
2nd		None		
3rd		None		
4th	Digoxin	0.5 mg.		
5th		0.5 mg.		
6th		0.75 mg.		
7th		1.0 mg.		
8th		0.5 mg.		
9th		1.0 mg.		
10th		1.0 mg.		6.0
11th		1.25 mg.		
12th		0.75 mg.	Atrial flutter	
13th		None		4.9
14th		None	Atrial fibrillation	
15th		0.5 mg.	Normal sinus rhythm	
16th		1.0 mg.		
17th		0.5 mg.		
18th		None		5.0
19th	Digitalis leaf	0.3 Gm.		
20th		0.2 Gm.		
21st		None		
22nd		0.2 Gm.		5.6
23rd	Digoxin	0.5 mg.		
24th		1.0 mg.		4.8

DISCUSSION

A number of authors[1–5] have emphasized the rarity of atrial flutter due to digitalis intoxication. Others[6, 7] have merely remarked that any arrhythmia may be the result of too much digitalis and have usually referred to Katz[8] as the basis for this statement. Recent reviews[9–11] of digitalis toxicity fail to mention atrial flutter in this regard.

Authentic cases of arrhythmias due to digitalis intoxication should meet 3 criteria: the patient should develop the arrhythmia while taking digitalis; he should not be taking any other drugs known to cause cardiac arrhythmias; and the abnormal rhythm should disappear when the digitalis is discontinued. Atrial flutter due to digitalis intoxication must be carefully differentiated from paroxysmal atrial tachycardia with atrioventricular block, which is a much more common manifestation of digitalis intoxication. The absence in all leads of the continuous base line undulation so characteristic of flutter and the slower average atrial rate are the most important electrocardiographic features that distinguish paroxysmal atrial tachycardia with block.[12, 13] The latter is ordinarily a distinctive clinical entity which may usually be differentiated from atrial flutter not due to digitalis.[13]

Wedd,[14] in 1924, was apparently the first to report a case of atrial flutter due to digitalis intoxication. Eight years later, McMillan and Bellet[15] reported 2 more cases. Imelio and Taltavull[16] in 1940 and Zubillaga[4] in 1942, each added 1 case to the literature. Cole,[5] in 1950, while emphasizing diarrhea as a toxic effect of digitalis, presented a patient who developed atrial flutter after an overdosage of the drug. Bickel and associates[17] reported a transient episode of atrial flutter in a young

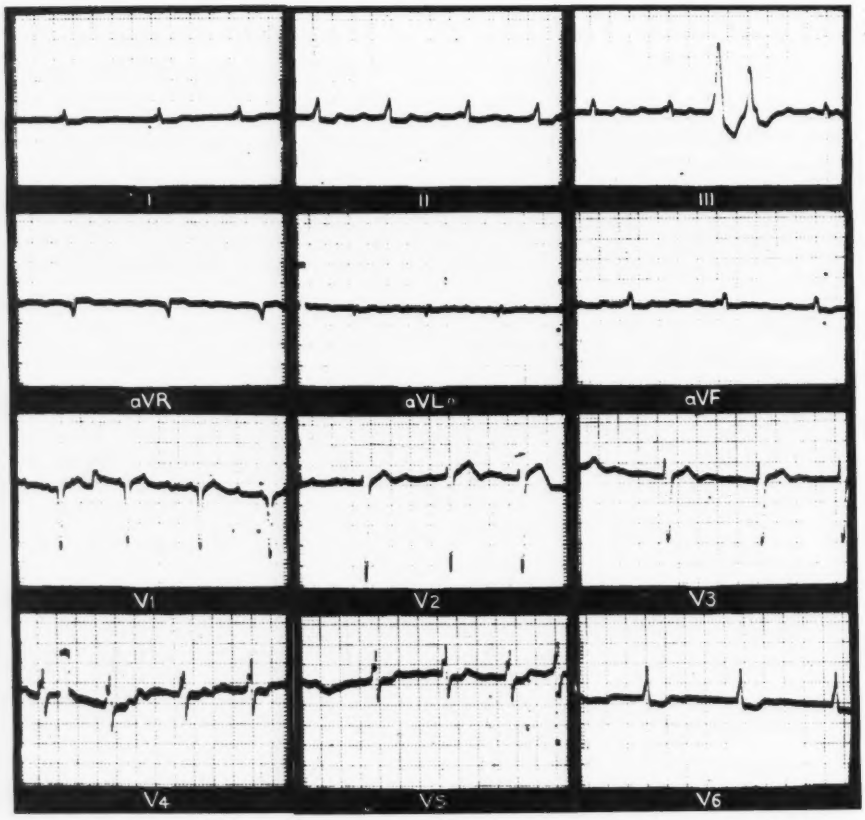


FIG. 1. Electrocardiogram showing atrial flutter with varying atrioventricular block and ventricular premature beats.

woman who tried unsuccessfully to commit suicide with 50 mg. of digitoxin. Hejtmancik, Herrmann, and Bradfield[18] mentioned 5 cases of atrial flutter produced by digitalis intoxication and found that the arrhythmias reverted to normal sinus rhythm after withdrawal of the digitalis. Unfortunately, these 5 cases are the only ones of the 15 in the literature in which electrocardiograms were not illustrated. The comment in the text that one of the cases showed several shifts from paroxysmal atrial tachycardia to flutter and back, strongly suggests that this may really have been a typical example of the several phases of paroxysmal atrial tachycardia with block due to digitalis intoxication. Lown and Levine[13] have recently commented on 3 cases of atrial flutter which they thought were unequivocally due to digitalis overdosage. Two of these cases were different from the other cases reviewed here in that both were known to have had atrial fibrillation as their basic rhythm before the flutter appeared. The presence of prior atrial irritability weakens the evidence for digitalis as the cause of flutter in these 2 cases; in the absence of digitalis intoxication, atrial fibrillation may often shift in and out of flutter.[3] Other clinical evidence in these 2 cases points to digitalis as a likely cause of the flutter, however.

The present case was an elderly man with arteriosclerotic heart disease and severe heart failure who developed atrial flutter with ventricular premature beats after a total dose of

7.25 mg. of digoxin during a 9-day period. This was probably an excessive amount if the average digitalizing dose of digoxin is considered to be 3.75 mg.[19] or even less[20] and the maintenance dose 0.25 to 0.75 mg.,[21] in view of the following coexisting factors, which lower digitalis tolerance: (1) the patient having taken digitalis leaf 0.2 Gm. per day up to 3 days previously, and this preparation possibly not having been fully excreted for 3 weeks,[12] (2) advanced age,[22, 23] (3) severe congestive heart failure,[22, 23] (4) renal disease,[22] and (5) a diuresis of 9 pounds with a probably significant potassium loss. Although serum levels do not necessarily indicate the magnitude of potassium shifts, it is noteworthy that the patient's serum potassium fell 1.1 mEq. per liter during the period of digoxin administration. Supplementary potassium was not given because of a rising blood urea nitrogen. Sampson, Alberton, and Kondo[24] were the first to point out that ectopic beats due to digitalis toxicity could be abolished by the administration of potassium even with normal serum levels. Numerous subsequent studies have confirmed this and have established that depletion of potassium sensitizes the heart to digitalis.[25–29]

When atrial flutter developed, the patient was also receiving aminophylline suppositories, tetracycline, and methylphenidate hydrochloride (Ritalin); these drugs are not known to cause this arrhythmia. Two days after digitalis had been discontinued the atrial flutter changed to atrial fibrillation and in 3 days normal sinus rhythm was again present. Lown and Levine[13] treated 2 patients with atrial flutter due to digitalis intoxication with intravenous potassium chloride, 35 and 40 mEq. respectively. They observed the same sequence, namely a period of atrial fibrillation before reversion to normal sinus rhythm in 10 and about 24 hours. Since it is well established that potassium loss causes atrial muscle to become refractory to vagal or other cholinergic influence, they presumed that while the administered potassium was counteracting the direct muscular effects of digitalis it was also restoring atrial responsiveness to the excitatory vagal effects with an interval of atrial fibrillation resulting. However, the same sequence took place in the present case without supplementary potassium administration. Further, such a sequence is of course common following digitalis treatment of ordinary atrial flutter.[30] Since digitalis facilitates potassium loss from the cardiac muscle cell, the similar sequence from flutter through fibrillation to sinus rhythm under these 3 different circumstances may reflect the reentry of potassium into the cell, either as the digitalis effect recedes or as serum potassium levels are raised. Of greater practical significance was the observed prompt dissolution of digitalis-induced atrial flutter by means of potassium administration, because ordinary flutter may not respond even to toxic doses of potassium.[13] This suggests that a therapeutic trial of potassium may be undertaken in instances of flutter in which digitalis intoxication may be implicated, provided no contraindications exist and proper safeguards are employed.

Several reports of atrial flutter associated with digitalis intoxication have not been included in this review as examples of flutter *due* to digitalis. Two papers concerning digitalis toxicity, one by Herrmann, Decherd, and McKinley[31] and the other by Crouch, Herrmann, and Hejtmancik[32] list 5 cases of atrial flutter occurring in patients who had digitalis toxicity but fail to mention whether these patients had arrhythmias before digitalization or if the arrythmias disappeared on withdrawal of the digitalis. Moreover, these patients may be the same as those mentioned in the previously cited paper by this group.[18] In a recent review Shrager[22] enumerated 3 cases of atrial flutter among 40 selected cases of digitalis toxicity but pointed out that these arrhythmias were associated with, and not necessarily caused by, the intoxication. In this regard, one should note that digitalization to the point of toxicity is often employed in patients with atrial flutter because the margin between the toxic dose and that required to achieve the therapeutic goal may be very narrow in these cases.[23] Two case reports[33, 34] of atrial flutter due to digitalis toxicity fail to

meet the criterion that the arrhythmia should disappear when the drug is stopped. Both these patients were given more digitalis and finally reverted to normal sinus rhythm while still taking digitalis.

The available information on the accepted cases of atrial flutter due to digitalis toxicity has been analyzed for clues as to when digitalis intoxication could be considered the cause of the flutter. The ages of the patients varied from 32 to 85 years. Of 12 cases, only 3 were female but this incidence is presumably coincidental, or perhaps reflects the male preponderance that has been noted in ordinary atrial flutter.[13, 18] The types of heart disease included syphilitic, rheumatic, and arteriosclerotic; 2 patients[5, 17] had normal hearts. With the exception of these 2 cases, the patients were in moderate to severe congestive heart failure. The digitalis preparation or route of administration did not appear to be significant variables. Data concerning serum potassium were lacking in most of these reports but, as far as could be determined, the administration of diuretics was not a possible cause of potassium loss when atrial flutter was developing except in 2 cases of Lown and Levine.[13]

Although the ventricular rate ranged from 66 to 160, all but 3 of the cases had rates near the lower figure. The degree of atrioventricular block varied from 2:1 to 12:1, but was usually of the higher degrees. Ventricular premature beats were observed in our patient and in at least 3 others in the literature; adequate tracings were usually not available for analysis. In untreated flutter of the ordinary type the ventricular rate is rapid because the atrioventricular block is usually 2:1 and ventricular premature beats have been stated to be rare.[12] The latter observation would be consistent with the fact that a rapid ventricular rate tends to suppress the intrusion of ventricular premature beats,[35] including those due to digitalis.[36] However, in one series of 40 patients with ordinary atrial flutter, 22 per cent showed ventricular premature beats.[13] The discrepancy may have been due to the presence of congestive heart failure, which may in itself be associated with ventricular premature beats.[37]

From these considerations digitalis intoxication may be suspected as the cause of atrial flutter when a patient with normal sinus rhythm develops atrial flutter with a slow ventricular rate after the administration of large amounts of digitalis. When the ventricular rate is rapid under such circumstances, the occurrence of ventricular premature beats also raises the possibility of digitalis overdosage, especially if congestive heart failure is not prominent. If there is reason to believe that the patient has recently lost potassium by diuresis or other means, this may be another helpful clue. Finally, even if serum potassium levels are normal and there is no clear-cut evidence of potassium loss, the prompt dissolution of a well-established flutter after a therapeutic trial of potassium points strongly to digitalis intoxication as a possible cause of the flutter.

Summary

Atrial flutter is a rare complication of digitalis intoxication. Only 15 fairly definite cases could be found in the literature.

A sixteenth case of atrial flutter due to digitalis toxicity is presented. The patient was an elderly man in severe congestive heart failure who received 7.25 mg. of digoxin during a 9-day period.

Digitalis as a cause of atrial flutter should be suspected when the arrhythmia is associated with ventricular premature beats, despite a rapid ventricular rate, if congestive heart failure is not marked. The same may be said of flutter that develops in the presence of a slow ventricular rate in a heavily digitalized patient with congestive failure. A therapeutic trial of potassium may be helpful in doubtful cases.

Summario in Interlingua

Flutter atrial es un complication rar de intoxication per digitalis. Solmente 15 casos definite poteva esser trovate in le litteratura.

Es presentate un dece-sexte caso de flutter atrial causate per toxicitate de digitalis. Le

patiente esseva un masculo de etate avantiate qui esseva in sever disfallimento cardiac congestive e recipeva 7,25 mg de digoxina durante un periodo de 9 dies.

Digitalis como causa de flutter atrial debera esser suspicite quando le arrhythmia es associate con prematur pulsos ventricular in respecto del accelerate frequentia ventricular, in casos in que le congestive disfallimento cardiac non es marcate. Le mesmo pote esser dicite con respecto a flutter que se disveloppa in le presentia de un lente frequentia ventricular in patientes con congestive disfallimento qui es fortemente digitalisate. Un proba therapeutic con kalium es a recommendar in casos de dubita.

REFERENCES

1. Friedberg, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders, 1956.
2. Levine, S. A.: Clinical Heart Diseases. Ed. 5. Philadelphia, W. B. Saunders, 1958.
3. Bellet, S.: Clinical Disorders of the Heart Beat. Philadelphia, Lea & Febiger, 1953.
4. Zubillaga, R.: Flutter auricular precipitado por una ampolleta de ouabaina en un paciente previamente digitalizado. Bol. Hosp. Caracas **41**: 145, 1942.
5. Cole, S. L.: Digitalis intoxication: Chronic effects manifested by diarrhea and auricular flutter. Am. Heart J. **39**: 900, 1950.
6. Cohen, B. M.: Digitalis poisoning and its treatment. New England J. Med. **245**: 225, 1952.
7. Segal, J. A.: Digitalis intoxication. Connecticut M. J. **19**: 803, 1955.
8. Katz, L. N.: Electrocardiography. Philadelphia, Lea & Febiger, 1941.
9. Burwell, W. B., and Hendrix, J. P.: Digitalis poisoning. Am. J. Med. **8**: 640, 1950.
10. Flaxman, N.: Digitalis poisoning. Am. J. M. Sc. **216**: 179, 1950.
11. Giuffra, L. J., and Tseng, H. L.: Some clinical aspects of digitalis intoxication. New York J. Med. **52**: 581, 1952.
12. Lown, B., and Levine, S. A.: Current concepts in digitalis therapy. New England J. Med. **250**: 771, 1954.
13. —, and Levine, H. D.: Atrial Arrhythmias, Digitalis and Potassium. New York, Landsberger, 1958.
14. Wedd, A. M.: Clinical auricular flutter. Ann. Clin. Med. **3**: 69, 1924.
15. McMillan, T. M., and Bellet, S.: Auricular flutter: Some of its clinical manifestations and its treatment. Am. J. M. Sc. **184**: 33, 1932.
16. Imelio, L., and Taltavull, R. J.: Calcificación pericárdica y flutter auricular digitálico. Rev. méd. Rosario **30**: 1195, 1940.
17. Bickel, G., Plattner, H., and Edelstein, H.: Intoxication digitalique massive terminée par la guérison. Arch. mal. coeur **44**: 61, 1951.
18. Hejtmancik, M. R., Herrmann, G. R., and Bradfield, J. Y.: Flutter auriculaire. Arch. mal. coeur **44**: 16, 1951.
19. Rose, O. A., Batterman, R. C., and DeGraff, A. C.: Clinical studies on digoxin, purified digitalis glycoside. Am. Heart J. **24**: 435, 1942.
20. Wayne, E. J.: Clinical observations on two pure glucosides of digitalis, digoxin and digitalinum verum. Clin. Sc. **1**: 63, 1933.
21. Batterman, R. C., and DeGraff, A. C.: Comparative study on use of purified digitalis glycosides, digoxin, digitoxin, and lanatoside C for management of ambulatory patients with congestive heart failure. Am. Heart J. **34**: 663, 1947.
22. Shrager, M. W.: Digitalis intoxication. Arch. Int. Med. **100**: 881, 1957.
23. DeGraff, A. C.: Digitalis intoxication. Circulation **9**: 115, 1954.
24. Sampson, J. J., Alberton, E. C., and Kondo, B.: Effect on man of potassium administration in relation to digitalis glycosides: With special reference to blood serum potassium, electrocardiogram, and ectopic beats. Am. Heart J. **26**: 164, 1943.
25. Baker, J. B. E.: The influence of calcium and potassium ions on the toxicity of ouabain. Brit. J. Pharmacol. **2**: 259, 1947.
26. Buff, I. E.: The use of potassium chloride and digoxin in congestive heart failure. South. M. J. **42**: 1037, 1949.
27. Enselberg, C. D., Simmons, H. G., and Mintz, A. A.: The effect of potassium upon the heart with special reference to the possibility of treatment of toxic arrhythmias due to digitalis. Am. Heart J. **39**: 713, 1950.
28. Lown, B., Salzberg, H., Enselberg, C. D., and Weston, R. E.: Interrelationship between potassium metabolism and digitalis toxicity in heart failure. Proc. Soc. Exper. Biol. & Med. **76**: 797, 1951.
29. —, Wyatt, N. F., Crocker, A. T., Goodale, W. T., and Levine, S. A.: Interrelationship of digitalis and potassium in auricular tachycardia with block. Am. Heart J. **45**: 589, 1953.
30. Bloomfield, A. L.: Treatment of auricular

flutter with digitalis. Am. J. Med. **7**: 437, 1949.

31. Herrmann, G. R., Decherd, G. M., and McKinley, W. F.: Digitalis poisoning. J.A.M.A. **126**: 760, 1944.
32. Crouch, R. B., Herrmann, G. R., and Hejtmancik, M. R.: Digitalis intoxication. Texas J. Med. **52**: 714, 1956.
33. Liccioni, H.: Caso de flutter auricular transitorio por intoxicación digitálica. Rev. Policlín. Caracas **10**: 192, 1941.
34. Dassen, R., Berreta, J. A., and Balbi-Robeco, J. M.: A propósito de un aleteo y fibrilación auricular de origen digitálico. Prensa méd. argent. **32**: 1093, 1945.
35. Langendorf, R., Pick, A., and Winternitz, M.: Mechanisms of intermittent ventricular bigeminy. I. Appearance of ectopic beats dependent upon length of the ventricular cycle, the "rule of bigeminy." Circulation **11**: 422, 1955.
36. Rothberger, C. J., and Winterberg, H.: Über den Einfluss von Strophanthidin auf die Reizbildungsfähigkeit der automatischen Zentren des Herzens. Pflüger's Arch. ges. Physiol. **150**: 217, 1913.
37. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias. London, Heinemann, 1953, p. 476.

John Wesley
Physician and Apothecary

Wesley emphasized the use of simple remedies. "Experience shows that one thing (one medicine at a time) will cure most disorders. Why administer more? Only to swell the apothecaries' bill? Nay, possibly on purpose: to prolong the distemper so that the doctor and apothecary may divide the spoil." Indeed those appear to be harsh words and sentiments from a man of the cloth.

Wesley established his "visitors of the sick" organizations in all his "Societies" of Methodists throughout England. He set up regular outpatient clinics in Bristol and in London. But wherever he went (and he travelled more than five thousand miles a year on foot and by horse) he saw the sick and prescribed for them within his abilities. In his absence from his clinics (he eventually made his peace with organized medicine of that day) he states in 1780 that "a physician is in regular attendance at the Chapel House in West Street (London) twice a week for three hours."

Wesley established his first clinic in 1746. One year later he decided the need for transmission of medical knowledge to the public had to be met. And he did so in his inimitable manner. He wrote a book "Primitive Physic" or "An Easy and Natural Method of Curing Most Diseases."—Alfred A. Weinstein. *John Wesley Physician and Apothecary.* The Georgia Review **10**: 3, 1956.

Atrial Septal Defect: Factors Affecting the Surgical Mortality Rate

By Dwight C. McGoon, M.D., H. J. C. Swan, M.B., Ph.D., Robert O. Brandenburg, M.D., Daniel C. Connolly, M.D., Ph.D., and John W. Kirklin, M.D.

Analysis of accumulated experience with the repair of atrial septal defect in 119 adults has revealed several factors determinable preoperatively that appear to have a strong influence on the operative risk. These factors are related to the presence of pulmonary vascular disease or heart failure and contribute importantly to the selection of patients for operation.

SURGICAL treatment for atrial septal defect has been practiced for approximately 5 years. The selection of patients for operation should be based upon a number of considerations, including knowledge of the operative mortality rate and factors influencing it. This study was undertaken for the purpose of gathering and interpreting data upon these matters.

Material

The records of patients 15 years of age or older who were operated upon by us before January 1958 for repair of an atrial septal defect have been analyzed. The first such operation in this institution was performed in February 1953. Patients having partial persistent common atrioventricular canal (so-called ostium primum defect) or the complete form of this malformation were not included herein; these were reported on previously.[1] Patients with associated abnormalities such as valvular pulmonary stenosis, ventricular septal defect, common atrium, or total anomalous pulmonary venous connection likewise were not included. Patients having partial anomalous venous connection of the right lung were considered to have a variant of simple atrial septal defect and were included. A total of 119 cases fulfilled these qualifications.

The notes concerning clinical findings were reviewed. Cardiac catheterization had been performed[2] preoperatively at the Mayo Clinic in 83 per cent of the cases and elsewhere in an additional 4 per cent. The observations at operation had been recorded in detailed notes, which were reviewed. All deaths that occurred during operation or during the period of postoperative hospitalization were considered operative deaths.

One hundred and eight of the patients had been operated upon by the atrial-well technic.[3] In 7 patients repair was made through open cardiotomy with extracorporeal circulation,[4] in most instances because of very high right atrial pressure. Four patients were operated upon by the Bailey technic[5] for miscellaneous reasons.

Results

Fourteen patients did not survive the operation or postoperative period in the hospital, for a total mortality rate of 12 per cent. In 2 of the nonsurvivors, repair was not carried out because a decrease in systemic arterial blood pressure and an increase in pulmonary arterial pressure occurred when the defect was temporarily occluded. In only 2 of the 14 cases were there obvious surgical technical factors that may have contributed significantly to the death. In 1 patient, operated upon by the atrial-well technic, there was severe postoperative hemorrhage into the thorax, probably causally related to the patient's death with hyperpyrexia and oliguria 48 hours after operation. In a second patient, the quantity of heparin administered during operation was inadequate.

The operative mortality in relation to the age of the patients is shown in table 1. The mortality rates in the various age groups are relatively uniform.

A decision as to whether or not congestive heart failure was present or had previously been present was usually made by the examining physician. It is fully realized that rigid

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

TABLE 1.—*Age and Hospital Mortality Rate*

Age (years)	Total patients	Hospital deaths	
		No.	Per cent
15-29	47	4	9
30-39	34	4	12
40-49	28	5	18
50 or more	10	1	10
Total	119	14	12

definition of heart failure from clinical criteria is impossible. If congestive heart failure had occurred, the mortality rate was 39 per cent whereas in its absence the mortality rate was 7 per cent (table 2).

Patients with a peak right atrial pressure of 15 mm. Hg or more, 10 in number, experienced a hospital mortality rate of 50 per cent (table 2). It was assumed that patients not catheterized had a peak right atrial pressure of less than 15 mm. Hg, an assumption which seems justified since all patients not catheterized had clinically and surgically uncomplicated septal defects and showed no evidence of heart failure or pulmonary hypertension.

The magnitude and direction of the shunt were determined in patients catheterized in our institution.[6] For all patients not catheterized it is assumed that the right-to-left shunt was less than 10 per cent, an assumption* that seems justified for the reasons already noted. This is the basis for the data concerning the magnitude of right-to-left shunt recorded in table 2. A striking difference exists between these 2 groups as regards operative mortality. In patients with a right-to-left shunt of 10 per cent or more, the hospital mortality rate was 50 per cent.

Fifty-three per cent of the patients with a systolic pressure of 75 mm. or more in the pulmonary artery were nonsurvivors, in contrast to a mortality rate of 4 per cent in patients with pulmonary arterial pressure of less than 75 mm. Hg. It was assumed that in patients not catheterized the systolic pressure in the pulmonary artery was 75 mm. or less, for the reason already noted.

*The percentage figure refers to that proportion of blood passing through the systemic circulation which is shunted blood.

In 45 patients data were available for calculations of total pulmonary resistance and total systemic resistance. The hospital mortality rate was 71 per cent for the 7 patients in whom the ratio of total pulmonary resistance to systemic resistance equaled or exceeded 0.5 (table 2). The use of this resistance ratio rather than the pulmonary resistance itself serves to minimize the effect of nonspecific factors, such as body size, and to allow a more accurate comparison of such data.

Table 3 lists individually the pertinent information on each of the 14 nonsurviving patients, which has already been assimilated in the figures presented in table 2.

COMMENT

The operative mortality rate encountered in this series for the repair of an uncomplicated atrial septal defect is less than 2 per cent, a risk so favorable that it approximates that of closure of an uncomplicated patent ductus arteriosus. In any condition the advisability of surgical treatment can be deduced only after careful consideration of the comparative risks of operative and nonoperative treatment. Because of the low operative risk established in this large group of patients operated upon by the atrial-well technic, we feel justified in advising that an atrial septal defect of significant size be repaired by this method even in the asymptomatic or minimally symptomatic patient.

The evidence at present available appears to indicate that closure of atrial septal defects in patients in whom pulmonary blood flow is clearly less than systemic blood flow will almost always result in death. The same appears true for patients with patent ductus arteriosus, aorticopulmonary fistula, common atrioventricular canal, and ventricular septal defect. Such patients are not accepted by us for closure of their intracardiac defects.

Only 1 of these 119 patients, who was operated upon early in the series, was inoperable by this criterion, and he failed to survive. Thirteen additional patients failed to survive. Since actual errors of surgical tech-

nic were rare, an inquiry into the factors that appear to have increased the risk of repair of atrial septal defect in the nonsurviving but theoretically operable patients is of importance. Better treatment of patients with these factors present should reduce the risk of repair for them in the future.

Age is the one factor so studied which does not appear per se to influence operative mortality strongly (table 1). It is amply demonstrated in table 2 that each of the factors listed there has a significant influence on the risk of the operation.

Rigid rules for the selection of patients for operation are seldom wise, for individual details must be appraised in each patient. The experience reported here, however, suggests that a clinical history of congestive heart failure, a markedly elevated right atrial pressure, a large right-to-left shunt, severely elevated pressure in the pulmonary artery, and markedly increased pulmonary vascular resistance adversely affect the operative risk in the group as a whole.

Furthermore, examination of each individual patient in an effort to determine the influence of abnormal values for these 5 factors that might affect the outcome of operation has yielded information of great practical clinical value. As recorded in table 4, if none or only 1 of these unfavorable factors exists in a given patient, the risk of operation is highly acceptable. The risk is very high when 2 such factors are present, and appears extreme in this series if 3 or more coexist.

Attention must of course be given to the probability that improvement in operative management or in preparation of the patient will reduce the mortality for the various categories of patients.

Two of the 5 pertinent factors are directly related to heart failure; these are a history of congestive heart failure and a markedly elevated right atrial pressure. Also, a large right-to-left shunt is probably indirectly related in most instances to right ventricular failure. Very high pulmonary arterial pressure is usually related to greatly increased pulmonary vascular resistance. Thus, there

TABLE 2.—*Influence of 5 Specific Factors on Operative Mortality*

Factor	Total no. of patients	Hospital deaths No.	Hospital deaths Per cent
History or evidence of congestive heart failure			
Present	18	7	39
Absent	101	7	7
Peak right atrial pressure			
15 mm. Hg or more	10	5	50
Less than 15 mm. Hg	109	9	8
Right-to-left shunt			
10 per cent or more	14*	7	50
Less than 10 per cent	105	7	7
Pulmonary hypertension			
75 mm. Hg or more, systolic	19	10	53
Clinically absent or less than 75 mm. Hg, systolic	100	4	4
Ratio of total pulmonary resistance to systemic resistance†			
0.5 or more	7	5	71
Less than 0.5	38	7	18

*In 3 of the 7 who survived, the pulmonary arterial systolic pressure was 40 mm. Hg or less, suggesting that the increased right-to-left shunt was due to some other factor than failure of the right side of the heart. If these 3 patients are excluded, the mortality rate in the group of 11 remaining patients with a right-to-left shunt of 10 per cent or more is 64 per cent.

†Sufficient data to allow calculation of resistances were available for only 45 patients. This is therefore a somewhat selected group, weighted with those patients for whom the advisability of operation was questioned.

appear to be 2 basically important and closely interrelated determinants of the factors which influence survival of the patient who undergoes operative closure of an atrial septal defect; namely, the presence or absence of excessively high pulmonary vascular resistance and the presence or absence of heart failure.

Increased Pulmonary Vascular Resistance. When prolonged excessive blood flow through the lungs occurs, resulting from a left-to-right shunt of blood, obstructive changes in the

TABLE 3.—*Five Factors Related to Operative Mortality in Patients Representing Surgical Deaths*

Death	History or presence of congestive heart failure	Right-to-left shunt, systemic blood flow (%)	Pulmonary-artery systolic pressure (mm. Hg)	Ratio of total pulmonary resistance to systemic resistance (breathing air)	Right atrial pressure (mm. Hg)	Left-to-right shunt, pulmonary blood flow (%)
1	Yes	38	86	.77	27/12	33
2	Yes	19	99	.73	35/23	21
3	No	47	138	>1.0	6/4	0
4	No	19	86	.55	4/-3	25
5	No	31	116	.7	10/4	28
6	No	16	107	.57	9/5	42
7*	No	?†	75	?	?	50
8	Yes	8	94	.39	9/4	57
9	Yes	0	114	.22	20/8	75
10	Yes	12	44	.1	12/4	80
11	Yes	0	50	.16	26/15	50
12	Yes	0	40	.12	25-30/7	68
13‡	No	0	76	.2	12/4	53
14‡	No	0	34	.1	8/1	63

*Catheterization done elsewhere—data incomplete.

†Reading of ear oximeter dropped from 93 at rest to 88 with exercise.

‡Death apparently due to technical factors.

pulmonary vasculature develop in some patients. The effect of increased pulmonary vascular resistance on hemodynamics and cardiac function differs significantly in the various congenital cardiac anomalies that permit a left-to-right shunt.

For example, in the presence of a large ventricular septal defect or a large aorticopulmonary communication the volume of blood shunted is a function of the relative pulmonary and systemic resistances. As the pulmonary resistance increases, a progressively smaller proportion of the pulmonary blood flow originates from the left ventricle.

In contrast, the volume of blood shunted through an atrial septal defect is only indirectly related to pulmonary vascular resistance, but rather is directly related to the relative volumes of blood that the right and left ventricles will accept from the atria during diastole. The atria can probably be regarded as a single reservoir for filling of the ventricle in the presence of an atrial septal defect of a size that does not materially restrict free flow of blood between the atria. The volume of blood entering either ventricle during diastole is dependent upon many factors, such as the relative impedance to the flow of blood offered at the mitral and tricuspid valves, and the completeness of emptying of each ventricle during systole. Probably most important are the relative volume distensibilities of the left and right ventricles, which are in part determined by the thickness and pliability of the ventricular walls. In the absence of markedly increased pulmonary vascular resistance and associated pulmonary hypertension the wall of the right ventricle is thinner and more distensible that that of the left ventricle, resulting in a large left-to-right shunt. Probably for the same reason, in the normal heart the end-diastolic pressure in the left ventricle is significantly higher than in the right. Thus, in the presence of an atrial septal defect, the hypertrophy of the right ventricle associated with the development of severe pulmonary hypertension may induce distensibility characteristics that more closely approximate those of the left ventricle, with concomitant reduction of the left-to-right shunt and the development of a right-to-left shunt.

There is a second contrast between the hemodynamic consequence of pulmonary hypertension in the presence of a ventricular septal defect and in the presence of an atrial septal defect. In the former, when pulmonary resistance is still low, the left ventricle has a large volume load imposed upon it, but as pulmonic resistance increases, the left ventricular volume load diminishes toward normal without a concomitant increase in its pressure load. It is never called upon to expel its blood against a resistance greater than that of the systemic vascular bed. Indeed, as pulmonary resistance climbs to excessive levels and a predominant right-to-left shunt appears, the strain imposed by the hemodynamic derangement shifts from the previously burdened left ventricle to the right ventricle.

However, in the case of an atrial septal defect, when the progressive increase in pul-

monary resistance is associated with a reduction in the volume of left-to-right shunt, the volume of blood pumped by the right ventricle is thereby lessened, but the total work load of the right ventricle remains increased above the normal level. Thus, in contrast to ventricular septal defect, the development of pulmonary hypertension in a patient with an atrial septal defect may not significantly lessen the encumbrance of the initially overburdened right ventricle.

Heart Failure. The data presented demonstrate that strong evidence for the presence of heart failure indicates a high operative risk for closure of an atrial septal defect. Therefore, it may be well to consider the mechanisms that result in heart failure in the presence of an atrial septal defect.[7]

Of nonsurvivors in this series, 4 of 14 patients exhibited signs of heart failure in association with severe pulmonary hypertension, and in each of these the volume load on the right ventricle had been much reduced by an increasing right-to-left shunt as well as by the reduction in volume of blood shunted from left to right.

Three patients exhibited strong evidence of heart failure in the absence of severe pulmonary hypertension, with large pulmonary blood flows and decreased pulmonary resistances. It may be significant that in 2 of these patients, marked tricuspid insufficiency was noted at operation, more severe than was noted in other patients in the series. Tricuspid insufficiency, of course, imposes a still greater volume load on the right ventricle.

Once chronic heart failure, from whatever cause, has occurred, the ability of that heart to regain compensation is apparently hampered, since any tendency to do so again increases the volume of the left-to-right shunt and thus the work of the right ventricle. Therefore, in certain patients it would seem inordinately difficult for the right ventricle to recover from a state of chronic failure, for not only is it unable to escape the burden of any existing pulmonary hypertension, but also, as it might tend to regain compensation, the volume load imposed upon it is increased.

TABLE 4.—*Relation of Over-all Operative Mortality Rate to Number of "Specific Factors" Present in Individual Patients*

Factors* present in patient	No. of patients	Mortality (%)
None	80	1.3
1	22	4.5
2	9	56
3	6	83
4	0	—
5	2	100

*The 5 adverse factors listed in table 2.

This does not pertain in the case of *acute* heart failure due to severe arrhythmia, to which these hearts are prone, and which may quickly subside with the return of normal rhythm.

SUMMARY

The data on 119 adult patients who had been operated upon by us for closure of an atrial septal defect were studied to determine what features determinable preoperatively bear upon the patient's ability to survive the operative period. Of the several factors so analyzed, 5 are significantly related to survival, namely, a history of clinical congestive heart failure, a markedly elevated right atrial pressure, a large right-to-left shunt, severely elevated pressure in the pulmonary artery, and markedly increased pulmonary vascular resistance. Each of these pertains to the presence of heart failure or excessive pulmonary vascular resistance. The mortality rate for repair of uncomplicated atrial septal defects by the atrial-well technic was less than 2 per cent.

SUMMARIO IN INTERLINGUA

Datos colligite in le casos de 119 patientes adulte operate per nos clauder un defecto del septo atrial esseva studiate con le objectivo de determinar qual factores de determinabilitate pre-operatori affice le capacitate del patientes de superviver al periodo del operation. Inter le varie factores analysate ab iste puncto de vista, 5 es significativemente relationate al question del superviventia. Illos es (1) un historia de clinic congestive disfallimento car-

diac, (2) un marcatemente elevate pression dextero-atrial, (3) un grande derivation dextero-sinistre, (4) un severmente elevate pression in le arteria pulmonar, e (5) marcate augmentos del resistentia pulmono-vascular. Omne iste factores es relationate al presentia de insufficientia cardiac o de excessos del resistentia pulmono-vascular. Le mortalitate in le reparo de non-complicate defectos del septo atrial, effectuate per medio del technica a puteo atrial, esseva quasi 2 pro cento.

REFERENCES

1. Cooley, J. C., and Kirklin, J. W.: The surgical treatment of persistent common atrioventricular canal: Report of 12 cases. Proc. Staff Meet. Mayo Clin. **31**: 523, 1956.
2. Wood, E. H.: Symposium on cardiac catheterization. Special technics of value in cardiac catheterization laboratory. Proc. Staff Meet. Mayo Clin. **28**: 58, 1953.
3. Gross, R. E., Watkins, E., Jr., Pomeranz, A. A., and Goldsmith, E. I.: Method for surgical closure of interauricular septal defects. Surg. Gynec. & Obst. **96**: 1, 1953.
4. Kirklin, J. W., Patrick, R. T., and Theye, R. A.: Theory and practice in the use of a pump-oxygenator for open intracardiac surgery. Thorax **12**: 93, 1957.
5. Bailey, C. P., Downing, D. F., Geckeler, G. D., Likoff, W., Goldberg, H., Scott, J. C., Janton, O., and Redondo-Ramirez, H. P.: Congenital interatrial communications: Clinical and surgical considerations with a description of a new surgical technique: Atrio-septo-pexy. Ann. Int. Med. **37**: 888, 1952.
6. Swan, H. J. C., Burchell, H. B., and Wood, E. H.: The presence of venoarterial shunts in patients with interatrial communications. Circulation **10**: 705, 1954.
7. Dexter, L.: Atrial septal defect. Brit. Heart J. **18**: 209, 1956.

Brofman, B. L., Charms, B. L., Kohn, P. M., Elder, J., Newman, R., and Rizika, M.: Unilateral Pulmonary Artery Occlusion in Man. Control Studies. J. Thoracic Surg. **34**: 206 (Aug.), 1957.

Temporary occlusion of the right or left main pulmonary artery was performed in over 100 patients by means of an especially designed triple-lumen cardiac catheter with an inflatable cuff. Pulmonary arterial flow to 1 lung was shut off for as long as 2 hours with no ill effects. In the control subjects there was no significant electrocardiographic change nor any important alteration in systemic blood pressure, oxygen saturation, cardiac output, or oxygen consumption. The main pulmonary artery pressure rose about 30 per cent but exhibited a slight fall on breathing 100 per cent oxygen, indicating further expansibility of the vascular tree. Apparently marked increases in unilateral flow (even to 5 times normal) are attended by significant decreases in pulmonary vascular resistance. Distal to the occlusion the pulmonary arterial pressure fell to about 8 mm. Hg, approximating pulmonary wedge pressure. Another indication of retrograde flow from the left atrium was the finding of high blood oxygen saturation. There was evidence of bronchial artery-pulmonary vascular communications in the control subjects. X-ray studies showed no change in vascular pattern during the period of main unilateral pulmonary artery occlusion.

Enselberg

Serum Cholesterol in Man: Diet Fat and Intrinsic Responsiveness

By Ancel Keys, Ph.D., Joseph T. Anderson, Ph.D., and Francisco Grande, M.D.

Data obtained from a number of dietary experiments in man yield a formula by which the responses in serum cholesterol to changes in diet can be predicted. In this paper the reliability of this formula is tested and the effects of various types of fatty acids on serum cholesterol are investigated.

THE serum cholesterol concentration in man is strongly influenced by both the amount and kind of fat in the diet and it is necessary to differentiate between at least 3 classes of fatty acids, saturated, monoenoic, and polyenoic. Furthermore, even on a fixed diet there are intrinsic differences between individuals. Finally, intraindividual variability is substantial as shown by spontaneous day-to-day variations. All these factors complicate the evaluation of the effects of the diet and the prediction of serum cholesterol responses to given dietary changes. However, the present paper will show that the average cholesterol responses of groups of men to changes of fat in the diet can be satisfactorily predicted from knowledge of the amounts of fat in the diet and that such prediction can be made even for groups of men who are relatively hypercholesteremic or hypocholesteremic.

Preliminary Prediction from 41 Sets of Data

As a first approximation we proposed[1] that the serum total cholesterol concentration be expressed as

$$Chol. = k + bS + cM + dP \qquad (1)$$

where k refers to all factors, other than the fats in the diet, that influence the cholesterol level and S, M, and P are, respectively, the percentages of the total calories in the diet supplied by glycerides of saturated, monoenoic, and polyenoic fatty acids. Actually, in the diets used, "monoenoic" is almost entirely oleic acid, while "polyenoic" is almost entirely linoleic acid. If everything else is constant, then, a change in the diet in respect to S, M, and P would produce a change in the cholesterol level:

$$\Delta\ Chol. = b\Delta S + c\Delta M + d\Delta P \qquad (2)$$

The values of the coefficients b, c, and d, may be estimated from experimental data on men who change their diets by the isocaloric exchange of fats for the carbohydrates of bread and jelly, or of one kind of fat for another, the diet being otherwise constant. In effect, for the solution of equation 2, we require a series of average serum cholesterol values of the same men on diets differing in respect to S, M, and P.

Accordingly, we carried out rigidly controlled experiments on groups of 12 to 27 men who exhibited no disorder of cholesterol metabolism. From the average values in 41 sets of comparisons, each involving one group of men on each of 2 diets for periods of 2 to 4 weeks, we obtained[2] the following values for the coefficients in equation 2: b = 2.74, c = 0, d = –1.31. Thus equation 2 becomes

$$\Delta\ Chol. = 2.74\ \Delta S - 1.31\ \Delta P \qquad (2A)$$

where Δ Chol. is measured in mg. per 100 ml. of serum.

The fats involved in the comparisons that yielded equation 2A, included butterfat, olive oil, cottonseed oil, sunflower seed oil, safflower

From the Laboratory of Physiological Hygiene, University of Minnesota, and the Hastings State Hospital, Minn.

The work reported here was aided by research grants from the National Dairy Council, Chicago, the Minnesota Heart Association, the Winton Companies Fund, Minneapolis, and the Schweppe Foundation, Chicago.

TABLE 1.—*Design of Experiment N. 6 Men in Each Group*

Group	Dietary Period				
	Days 1-28	Days 29-49	Days 50-70	Days 71-91	Days 92-112
W	H	SO	X	X	CO
Y	H	CO	X	X	SO
X	H	X	SO	CO	X
Z	H	X	CO	SO	X

H, house; SO, safflower oil; CO, corn oil.

Diets X maintained the constancy of calories and proteins but involved other variables not considered here.

oil, and the mixed fats of ordinary American diets at several levels of fat concentration. Comparisons involving corn oil in the diet were not included because of evidence that part of the effect of corn oil on the serum cholesterol concentration may be dependent on some factor other than the fatty acid in it.[3]

Since equation 2A was published, we have carried out a critical experiment with 22 men to check the question of the effect of dietary monoene on the serum cholesterol level.[4] It was found that the isocaloric substitution of 68 Gm. of oleic acid glyceride in the daily diet for carbohydrate, and vice versa, had no effect whatever. Since the only monoene contained in appreciable amount in all ordinary diets is oleic acid, it appears that the value of $e = 0$ in equation 2 is well demonstrated.

Equation 2A satisfactorily fitted the average cholesterol changes observed in the experiments that provided the data used in the derivation, with a coefficient of correlation of $r = 0.978$ between the 41 observed averages and those predicted. But it is important to examine equation 2 with additional experimental data, to consider the case of corn oil, and to evaluate the situation with men who differ intrinsically in their cholesterol levels on a given diet.

METHODS AND SUBJECTS

As in experiments previously reported,[2-5] all experiments were conducted with strict 24 hour dietary control, and blood samples were drawn for analysis at least twice from each man in the last days of each dietary period. Serum total cholesterol was measured by the method previously described.[6] The subjects were stabilized schizophrenic men who were physically healthy and were maintained on a regimen of constant activity. They were weighed, nude, in the basal state each week and the total calorie consumption was individually adjusted by adding or subtracting bread, jelly, and dry breakfast cereal from the standard measured ration to maintain constancy of body weight. Actual food intakes, minus any plate waste, were recorded for each man for each meal.

TABLE 2.—*Experiment N. Mean Dairy Calories, Protein and Total Fat Eaten on the Diets, Together with Mean Body Weights at the End of the Dietary Periods*

Item	Group WY	Group XZ
Number of men	12	12
Age	**51.3**	**50.6**
Body weight, Kg. diet H	67.5	67.4
Body weight, Kg., diet SO	67.8	67.7
Body weight, Kg., diet CO	67.7	67.5
Calories, diet H	3180	3130
Calories, diet SO	3210	3160
Calories, diet CO	3180	3160
Protein, Gm., diet H	98.9	98.7
Protein, Gm., diet SO	98.8	98.6
Protein, Gm. diet CO	99.5	102.9
Total fat, Gm., diet H	137.4	136.3
Total fat, Gm., diet SO	136.8	134.8
Total fat, Gm., diet CO	137.5	135.3

H, house; SO, safflower oil; CO, corn oil.

In all the experiments reported here the men were divided into matched subgroups and subsisted on the experimental diets in a cross over or switchback arrangement. This is illustrated by the design of experiment N, given in table 1.

Food actually eaten was recorded for each man and the nutrient contents, including fatty acids, were calculated from tables of average values for each food item. The experimental fats were analyzed independently in each case, and, in the case of the more recent experiments (since 1955) including the new experiment series N and P, the fats in samples of the whole diets, as eaten, were extracted and analyzed directly for fatty acid composition.

Series N Experiments

The design of the N series of experiments is given in table 1. Note that this comprises 2 independent sets of experiments on 2 different groups of 12 men each, each group being subdivided into 2 subgroups who made their safflower oil vs. corn oil dietary changes in reverse order so that any time trend independent of the diet was automati-

cally compensated for. This cross over arrangement was not feasible in the case of the H diet but the relative stability of the cholesterol values in repeated samplings indicates that no large time trend was present.

Table 2 shows the mean values for calories, proteins, and total fats in the diets and the body weights at the ends of the dietary periods in the N series. Table 3 gives the mean intakes of glycerides of saturated, monoenoic, and polyenoic fatty acids. Table 4 gives the serum cholesterol values (means of duplicates) for each of the 24 men on each of 2 occasions on each of the 3 types of diets.

Analysis of 19 Additional Sets of Comparisons

The basic data of 10 sets of experiments involving corn oil or fish oil have been published elsewhere,[2] but were not used in the derivation of equation 2A. Full data on 3 sets of new experimental comparisons (the P series) have also been published.[4] Table 5 summarizes these data, as well as the 6 sets of comparisons from the N series, in a form suitable for application to equation 2.

We have shown that a small part of the effect on serum cholesterol of corn oil is apparently attributable to the larger amount of nonsaponifiable matter in this oil as compared with the other fats tested.[3] When fed at the level of 100 Gm. daily in a diet balanced at about 3,200 calories, as in the experiments involving corn oil in table 5, an average depression of about 6 mg. cholesterol per 100 ml. serum is attributable to the excess nonsaponifiable matter (phytosterol) in the corn oil. Accordingly, table 5 allows for this fact in the column of predicted "Δ Chol., corrected."

It is clear that equation 2A provides satisfactory prediction of the average cholesterol changes observed in these 19 sets of experiments, and that this is improved by allowing for the nonsaponifiable matter in corn oil. The standard error of estimate was calculated as SEE $= (\Sigma\ \Delta^2/N)^{\frac{1}{2}}$ where Δ is the discrepancy between observed and predicted changes in cholesterol concentration in the serum and N is the number of pairs (19). The result with equation 2A is SEE $= \pm 7.1$ mg. per 100 ml. With use of the prediction corrected for the nonsaponifiable matter in corn oil (when applicable), the value is SEE $= \pm 5.1$.

A completely independent solution of equation 2 with the method of least squares was obtained by using the observed raw data as given in table 5 and again using these data corrected by 6 mg. per 100 ml. in the case of the corn oil experiments. In both cases the value of the coefficient c in equation 2 was found to be statistically not different from zero. The results of the least squares solutions of the regression equation are given in table 6 for the 19 sets of observed data of table 5,

TABLE 3.—*Experiment N. Mean Intakes of Glycerides of Saturated, Monoene, and Polyene Fatty Acids*

Group	Diet	Saturated Gm./day	Saturated % Cal.	Monoene Gm./day	Monoene % Cal.	Polyene Gm./day	Polyene % Cal.
WY	H	65.9	18.6	61.9	17.5	10.7	3.0
WY	SO	29.3	8.2	26.4	7.4	81.1	22.8
WY	CO	33.6	9.5	42.4	12.0	61.5	17.4
XZ	H	64.6	18.5	61.1	17.5	10.6	3.0
XZ	SO	28.8	8.2	25.7	7.3	80.3	22.8
XZ	CO	32.8	9.3	41.5	11.8	61.0	17.3

H, house; SO, safflower oil; CO, corn oil.

for these data corrected by 6 mg. in the cases where corn oil was involved, and also for the 15 sets of data when the comparisons with the H diets were omitted (because a switchback design was not employed to eliminate all possibility of artefact by time trend). The latter solution with 15 sets of data avoids any possibility of error from uncompensated time trends in the comparisons involving the H diets.

The coefficients obtained in the 4 solutions are statistically not different from each other or from those in the previous solution (eq. 2A) from the data in 41 different sets of experiments. A test of the homogeneity of variances indicated that the data in table 5 may be considered to be homogeneous with those in the previously reported 41 sets (table VII),[2] so it was considered justifiable to pool the entire material of 60 sets of data. The method of least squares was used to obtain another solution for equation 2A, with use of the raw data of the 60 sets. This yielded

$$\Delta\ Chol. = 2.73\ \Delta S - 1.30\ \Delta P \qquad (2B)$$

When the corrected Δ Chol. values for the experiments involving corn oil were used, the 60 sets of data yielded the solution

$$\Delta\ Chol. = 2.68\ \Delta S - 1.23\ \Delta P \qquad (2C)$$

The standard errors of estimate for equations 2B and 2C were calculated from the differences between observed and predicted Δ Chol. and it was found that SEE $= \pm 5.79$ for equation 2B and SEE $= \pm 4.88$ for equation 2C. The standard errors of the 2 coefficients in equation 2B are $SE_b = \pm 0.086$, $SE_d = \pm 0.100$, and in equation 2C, $SE_b = \pm 0.084$, $SE_d = \pm 0.073$.

Intrinsic Differences Among Men

The data in table 4 illustrate the well known fact that even on exactly the same diet and when other conditions in the mode of life are standardized, there are consistent differences in serum cholesterol level among individual men. Subjects

TABLE 4.—*Serum Total Cholesterol Values, Mg. per 100 Ml., for the 24 Men in the N Series of Experiments*

Subject	Diet H		Diet SO		Diet CO	
	Day 26	Day 30	Day 19	Day 21	Day 19	Day 21
W1	232	249	142	160	146	142
W2	207	222	150	154	163	162
W3	176	184	134	128	138	137
W4	220	231	172	166	164	160
W5	270	276	179	177	178	190
W6	227	224	192	180	188	180
Y1	204	202	180	184	179	164
Y2	219	230	178	184	180	174
Y3	235	228	170	159	186	172
Y4	184	178	154	170	151	150
Y5	170	164	137	140	131	126
Y6	188	176	142	138	128	126
Mean	211.00	213.66	160.83	161.66	161.00	156.91
Grand mean	212.33	±6.23	161.25	±3.86	158.95	±4.28
X1	174	179	129	132	153	144
X2	182	166	138	142	140	134
X3	256	241	196	200	199	204
X4	214	206	148	152	149	144
X5	208	196	160	156	161	162
X6	213	210	175	170	178	172
Z1	196	189	128	126	150	152
Z2	179	160	144	142	142	137
Z3	149	137	120	119	122	121
Z4	288	304	227	226	230	236
Z5	235	234	188	183	195	190
Z6	168	172	133	134	140	142
Mean	205.16	199.50	157.16	156.83	163.25	161.50
Grand mean	202.33	±8.44	157.00	±7.68	162.37	±6.46

The number of days of subsistence on each type of diet is indicated at the heads of the columns.

W5 and Z4, for example, are consistently relatively hypercholesteremic while subjects Y4 and Z6 are consistently low in cholesterol level. But do such men differ in responsiveness to a dietary change?

This question can be examined by comparing the magnitudes of the serum cholesterol responses, to a given dietary change, of experimental subjects classified according to their cholesterol values on a given control diet. This has been done by subdividing the 24 men in the N series into 2 groups of 12 men each. The "higher" group averaged 235.3 mg. per 100 ml. on the H diet and exhibited an average fall of 58.7 on the SO diet; the "lower" group had corresponding averages of 179.4 and 37.8 mg. per 100 ml. These results are given in table 7 together with a similar analysis of the data published by Starke[7] on 154 patients on a control diet and again after subsistence on a rice-fruit diet. Both sets of data show an important relationship between responsiveness and the intrinsic (control) level of cholesterol.

Theoretically, to some extent such a difference in "responsiveness" could be more apparent than real. With a single measurement of serum cholesterol on the H diet, both random intraindividual variability and measurement error would combine to group overestimates in the "higher" group and underestimates in the "lower" group. Then a second measurement on the SO diet, with both sources of variation again acting at random, would tend to show larger Δ Chol. in the "higher" than in the "lower" group, even if there were, in fact, no real relationship between intrinsic level and Δ Chol. But this possibility can be eliminated by a more elaborate analysis of the data in table 4.

Comparison of the serum cholesterol values on the first and second occasions of blood drawing on a constant diet will reveal the magnitude of any such artefactitious trend. This comparison may be made by solving, with the method of least squares, the regression equation, $Y = a + bX$, where X is the value on the first occasion, Y is that predicted for the second occasion, a and b are the intercept and slope of the regression line, respectively. Table 8 shows that on each of the 3 diets the slope of the regression line relating the first to the second blood samples is not significantly different from unity and therefore there is no significant artefactitious trend.

Table 8 also shows the results of this regression analysis applied to the prediction of the individual cholesterol values on the SO and CO diets from the cholesterol values of the same individuals on the H diet. In all cases the slope, b, is different from unity with high significance.

The regression constants in table 8 pertain only to the data of table 4. It is more convenient to make the analysis in percentage terms which have general application:

$$\Delta\% = a + bX\% \qquad (4)$$

where X% is the cholesterol value of an individual expressed as a percentage of the mean of a group or population on the same given diet, and Δ% is the predicted cholesterol change of that individual in response to a particular diet change, again expressed as a percentage of the mean change of the group undergoing the same dietary alteration. In these terms, for the data of table 4, we have the following solution for equation 4: H to SO, $a = -73$, $b = 1.73$; H to CO, $a = -64$, $b = 1.64$. Note that $\Delta\% = 100$ when $X\% = 100$ and $a = 100\ (1\text{-}b)$.

Table 9 summarizes 3 more sets of original data suitable for analysis in the above terms. Four blood samples were drawn, on different days, from

TABLE 5.—*Mean Differences between % of Calories Provided by Glycerides of Saturated (ΔS), Monoene (ΔM), and Polyene (ΔP) Fatty Acids, Together with Mean (and S.E.) Serum Total Cholesterol Differences (Δ Chol.) Observed and Predicted from Equation 2A*

No. men	Expt. series	Diet comparison	ΔS	ΔM	ΔP	Δ Chol. (mg. %)		
						Observed	Predicted	Corr. Pred.
13	HWX	Cottonseed-Corn Oil	3.4	− 2.2	− 1.5	19.3±4.2	11.3	17.3
14	JWX	Butterfat-Corn Oil	11.7	1.0	−13.5	45.1±3.6	49.7	55.7
14	JWX	Olive-Corn Oil	0.3	12.1	−12.6	27.2±3.6	17.3	23.3
14	JWX	Sunflower-Corn Oil	− 0.2	− 1.9	1.5	10.2±2.8	1.5	7.5
12	JYZ	Cottonseed-Sardine Oil	0.6	0.1	− 0.7	3.9±5.2	2.5	2.5
12	JYZ	Olive-Sardine Oil	− 3.3	16.4	−13.0	10.1±4.6	8.0	8.0
12	JYZ	Sardine-Corn Oil	3.6	− 2.7	− 0.7	20.1±3.8	10.8	16.8
12	JYZ	Olive-Corn oil	0.3	13.7	−13.7	30.2±5.6	18.7	24.7
12	JYZ	Butterfat-Corn Oil	13.2	1.4	−14.8	59.5±5.7	55.6	61.6
12	JYZ	Butterfat-Sardine Oil	9.6	4.1	−14.1	39.4±5.6	44.8	44.8
12	NWY	House-Safflower	10.4	10.1	−19.8	51.1±7.1	54.4	54.4
12	NWY	House-Corn Oil	9.1	5.5	−14.4	53.4±6.2	43.8	49.8
12	NWY	Safflower-Corn Oil	− 1.3	− 4.6	5.4	2.3±2.7	−10.6	− 4.6
12	NXZ	House-Safflower	10.3	10.2	−19.8	45.3±4.2	54.1	54.1
12	NXZ	House-Corn Oil	9.2	5.7	−14.3	40.0±3.8	43.9	49.9
12	NXZ	Safflower-Corn Oil	− 1.1	− 4.5	5.5	− 5.4±2.4	−10.2	− 4.2
22	P	Olive Oil-Low Fat	4.1	20.1	2.6	12.5±4.4	14.4	14.4
22	P	Safflower Oleo.-Low Fat	4.2	2.0	2.6	12.5±4.5	14.9	14.9
22	P	Safflower Oleo.-Olive Oil	0.1	−18.1	0	0±3.1	0.3	0.3

The last column gives the predicted values when allowance is made for an average of 6 mg. % cholesterol depression for nonsaponifiable matter in corn oil when this oil comprises about 28% of total calories.

each man in the third and fourth weeks of subsistence on fixed control diets (not identical in the 3 experiments). Two to 4 more blood samples were drawn, again on different days, after several weeks of subsistence on another diet, variously low in total fat or involving substitution of a vegetable oil for saturated fats, in the several experiments. Calory equilibrium was maintained throughout and each blood sample was analyzed, in duplicate, for serum cholesterol. Table 9 gives the means of these duplicates for each individual, expressed as percentages of group means in the control period and as percentages of the group mean changes in the experimental period to facilitate analysis in the form of equation 4.

In all 3 experiments it was found that the cholesterol response to the dietary change was linearly related to the intrinsic level of the individuals as indicated by their values on the control diet. The slopes of the least-squares regression lines, in equation 4, were b = 1.92, b = 1.93, and b = 1.59 in experiments V, VII, and IX, respectively.

The applicability of equation 4 to other groups of persons and to other situations producing serum cholesterol changes may be checked with data in the literature. Individual "before" and "after" serum total cholesterol values are provided by Hatch et al.[8] on 24 hypertensive men changed to a rice-fruit diet, by Best et al.[9] on 14 men before and during daily sitosterol treatment, and beta lipoprotein cholesterol values by Farquhar and Sokolow[10] on 15 patients before and after substitution of safflower oil for a fixed part of the saturated fats in the diet. The findings from these data are summarized in table 10, which also gives the comparable figures from the original data of the present paper.

The estimates of the slope, b (± S. E.), are given in table 10. None of these differs significantly from each other. The largest difference, that between the series of Hatch et al. (b = 2.80) and experiment IX (b = 1.59), has a standard error of ±0.79, which gives a t value of 1.53. Since for a probability of 0.1 the required t value is 1.7, the difference is insignificant.

A good general estimate for the slope, b, would be the weighted mean of all 8 estimates in table 10, with the number of persons in each series used as the weights. This weighted mean is b = 1.91. Accordingly, we have

$$\tilde{\Delta}\ \% = 1.91\ X\% - 91 \qquad (4A)$$

It may be noted that the individual data of Starke[7] are not available for a least-squares solu-

TABLE 6.—*Solutions of Equation 2, Δ Chol. = $b\Delta S + d\Delta P$, with the Data in Table 5*

Data	Sets of data	b	d
Raw	19	2.65	—1.33
Corrected	19	2.39	—1.27
Raw	15	2.67	—1.43
Corrected	15	2.41	—1.31

"Raw" uses the observed data without changes; "Corrected" uses the same data but allows 6 mg. of cholesterol per 100 ml. for the effect of extra non saponifiable matter in corn oil. The solutions with only 15 sets of data were obtained by omitting comparisons involving the H diets in the N series of experiments.

tion of equation 4, but the means of the 2 groups allow a solution by simultaneous equations. The result is

$$\bar{\Delta}\ \% = 1.99\ X\% - 99 \qquad \textbf{(4B)}$$

which is in good agreement with equation 4A.

General Prediction of Response to Dietary Change

Equation 2C (and 2B) was derived from data on men with a narrow range of group average intrinsic cholesterol values. On a diet of the current American type, with S about 20 and P about 3 (per cent of total calories), these group averages were in the range of 215 to 235 with a grand average of about 225. Equation 4A shows the relative difference in response to diet of men who differ intrinsically in cholesterol level. Hence, from the information from equations 2C and 4A, it is now possible to formulate a general prediction of cholesterol responses to change in dietary fat.

Let Z_1, Z_2, and Z_3 refer to the average serum cholesterol values of a reference group of men on diets characterized by S_1, P_1; S_2, P_2; and S_3, P_3, respectively, the reference group being so defined that they will have $Z_1 = 225$ when $S_1 = 20$ and $P_1 = 3$. In other words, equation 2C will apply strictly to this reference group, and for such a reference group a change from a diet with $S_1 = 20$, $P_1 = 3$ to a second diet represented by S_2, P_2, should result in an average serum cholesterol change, as predicted by equation 2C, of Δ Chol. $= Z_2 - 225 = 2.68\ (S_2 - 20) - 1.23\ (P_2 - 3)$.

For another group of men, let G_1, G_2, and G_3 refer to their average cholesterol values on the above diets (S_1,P_1; S_2, P_2; S_3, P_3), where $G_1 \neq 225$ when $S_1 = 20$ and $P_1 = 3$. These men, in other words, are intrinsically different from the reference group to whom equation 2C applies without correction.

Now consider the situation where G_2 has been measured on a diet with S_2 and P_2 and it is desired to predict the value of G_3 when the diet is changed to S_3 and P_3. In order to correspond with the form of equation 4A, it is necessary to put the cholesterol values into percentage terms: $X\% = 100\ G_2 / Z_2$ and change from diet 2 to diet 3, $\Delta\% = 100\ (G_3 - G_2) / (Z_3 - Z_2)$.

These expressions may be put into equation 4A:

$$\Delta\% = 100\ (G_3 - G_2 / (Z_3 - Z_2) = 1.91\ (100\ G_2) / Z_2 - 91 \qquad (4C)$$

which may be rearranged:

$$G_3 = 0.91\ (Z_2 - G_2 - Z_3) + 1.91\ G_2\ Z_3 / Z_2 \qquad (4D)$$

The values of Z_2 and Z_3 necessary for the solution of equation 4D are found by the application of equation 2C, using the reference value of $Z_1 = 225$ when $S = 20$ and $P = 3$:

$$Z_2 - 225 = 2.68\ (S_2 - 20) - 1.23\ (P_2 - 3) \qquad (2D)$$

whence

$$Z_2 = 175 + 2.68\ S_2 - 1.23\ P_2 \text{ and}$$
$$Z_3 = 175 + 2.68\ S_3 - 1.23\ P_3 \qquad (2E)$$

As an example of the calculation, take the case where $G_2 = 300$ when $S_2 = 25$, $P_2 = 4$, and it is desired to predict G_3 when $S_3 = 10$, $P_3 = 10$. In this case we have

$$Z_2 = 175 + 2.68\ (25) - 1.23\ (4) = 237.1$$
$$Z_3 = 175 + 2.68\ (10) - 1.23\ (10) = 195.6 \text{ and}$$
$$G_3 = 0.91\ (237.1 - 300.0 - 195.6) + 1.91\ (300)\ (195.6) / (237.1) = 235.8$$

TABLE 7.—*Serum Cholesterol Responses (Means and Standard Errors) to Given Dietary Changes of Subjects Classified as "Higher" and "Lower" in Cholesterol Level on a Control Diet*

	Series A		Series B	
No. of persons	Higher 12	Lower 12	Higher 125	Lower 29
Control Chol., mg. %	235.3±7.7	179.4±5.3	289±4.1	199±3.2
Expt. Chol., mg. %	176.6±6.2	141.6±4.9	209±4.0	166±4.9
Δ Chol., mg. %	58.7±5.4	37.8±4.5	80±5.7	33±5.8

Series A is from the data of table 4, "Control" being the H diet and "Expt." being the SO diet; Series B is from Starke[7] for patients on a control diet and after change to a rice-fruit diet.

Test of Predictions with Published Data

There are surprisingly few data in the literature suitable for test of equations 2E and 4D (or 2C and 4A). Malmros and Wigand[11] have reported data from 4 dietary experiments on "healthy volunteers" and these are summarized, together with predictions, in table 11. In the first 2 of those

TABLE 8.—*Values for the Slope b (±S.E.), and the Intercept a in the Least-Squares Solution of $y = a + bX$, where X is Serum Cholesterol on One Occasion and y is That Predicted for the Same Man on a Second Occasion, Calculated from the Data in Table 4*

Diets compared	N	a	b
H_2 vs. H_1	24	−25.2	1.11±0.06
SO_2 vs. SO_1	24	9.7	0.94±0.06
CO_2 vs. CO_1	24	− 5.9	1.02±0.05
H_2, SO_2, CO_2 vs. H_1, SO_1, CO_1	72	− 5.3	1.02±0.03
SO_1 vs. H_1	24	20.3	0.67±0.09
SO_2 vs. H_2	24	68.5	0.44±0.08
SO_1, SO_2 vs. H_1, H_2	48	35.2	0.60±0.06
CO_1 vs. H_1	24	37.9	0.60±0.08
CO_2 vs. H_2	24	58.1	0.49±0.07
CO_1, CO_2 vs. H_1, H_2	48	29.7	0.63±0.05
SO_1, SO_2, CO_1, CO_2 vs. H_1, H_2	96	32.4	0.61±0.04

H, house; SO, safflower oil; CO, corn oil. Subscripts indicate the occasions. N, number of comparisons.

experiments the dietary periods were long enough (4 weeks each) to assure approximation to a cholesterol plateau, but in the other experiments the periods are too short (1 to 2½ weeks) to be sure on this score.

The predictions in table 11 make no allowance for the cholesterol-lowering effect of the nonsaponifiable matter in corn oil. A reasonable estimate of this effect would be about 6 to 8 mg. of cholesterol per 100 ml. If this is included, the predicted Δ Chol. values (line 11 of table 11) would be +54, −61, −15, and −19. While the prediction may tend to exceed the observed Δ Chol. values, especially in experiment 1, it appears that the same general relationships hold for the volunteers in Lund, Sweden, as for the Hastings subjects in Minnesota.

The data published by Farquhar and Sokolow[10] do not include fully adequate details for the "control" diet eaten by their patients but an approximate test is possible. Fats provided an average of 41 per cent of the calories in the control diet and 95 per cent of these fats were from animal sources or were hardened vegetable fats. The experiment consisted of supplanting 30.8 per cent of the fat calories in the control diet by safflower oil. On the presumption that the control diet conformed to the usual American food pattern, a rough estimate is that the average composition of the fats in the control diet was about 50 per cent saturated and from 6 to 8 per cent polyunsaturated. The safflower oil used to supplant these fats in the amount of 30.8 per cent of the total calories contained 6 per cent saturated and 73 per cent polyunsaturated fatty acids. Accordingly, if the patients of Farquhar and Sokolow were like our

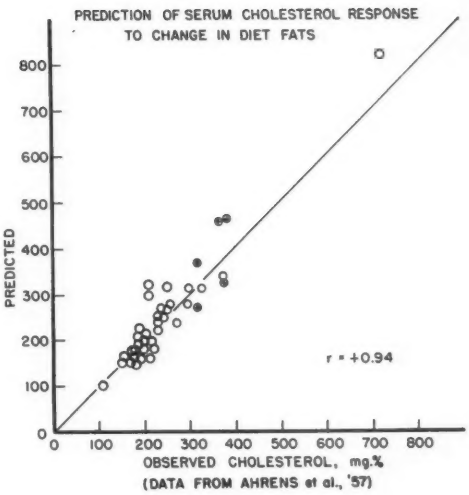


FIG. 1 *Top.* Observed and predicted individual serum cholesterol values following dietary change by the men studied by Ahrens and others.[12] The circles with crosses correspond to data from patients 13 and 15 whose cholesterol values were unusually resistant to dietary effects.

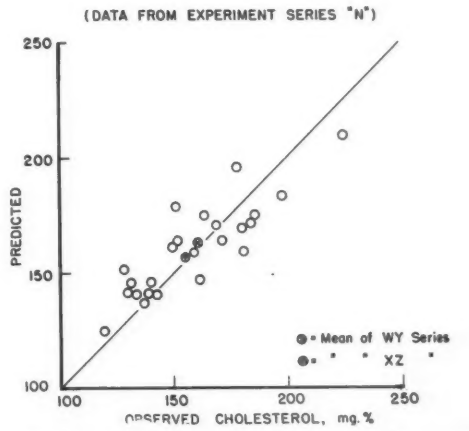


FIG. 2 *Bottom.* Observed and predicted individual serum cholesterol values for the men in experiment N.

own subjects, the change from the control to the safflower oil diet would produce an average serum total cholesterol change of Δ Chol. = 0.308 [2.68 (6 − 50) − 1.23 (73 − 7)] = − 59 mg. %. Farquhar and Sokolow reported an average change of − 52 ± 5.8 mg. of beta lipoprotein cholesterol per 100 ml. with no change in the alpha fraction. Hence we have observed Δ Chol. = − 52, predicted Δ Chol. = − 59.

TABLE 9.—*Individual Serum Total Cholesterol Values, X, and the Changes, Y, in Response to Diet Changes, Expressed as Percentages of the Mean Values for the Group*

Experiment V			Experiment VII			Experiment IX		
Subject	X	Y	Subject	X	Y	Subject	X	Y
F 1	85	111	H 1	91	57	J 1	84	60
F 2	96	120	H 2	96	84	J 2	104	100
F 3	96	31	H 3	107	133	J 3	75	63
F 4	78	88	H 4	76	87	J 4	77	90
F 5	96	74	H 5	140	181	J 5	83	76
F 6	91	111	H 6	105	103	J 6	126	127
F 7	120	125				J 7	99	72
F 8	80	54						
F 9	103	134						
F10	114	151	H10	119	199			
F11	88	43	H11	83	72	J11	111	132
F12	92	94	H12	77	63	J12	118	137
F13	74	29	H13	101	145	J13	84	60
F14	129	120	H14	118	124	J14	101	127
F15	139	211	H15	109	15	J15	84	97
F16	109	100				J16	120	90
F17	127	142				J17	115	111
F18	85	63						
			H19	118	165			
			H20	100	115			
			H21	95	145	J21	87	60
			H22	94	63	J22	98	102
			H23	100	39	J23	125	178
			H24	112	94	J24	104	74
						J25	103	127
						J26	117	118
			H28	93	148			
			H29	110	48	J29	100	130
			H30	110	169	J30	87	74
			H31	86	103	J31	111	139
			H32	72	18	J32	88	70
			H33	88	30	J33	106	116
						J34	92	70
Mean (mg. %)	(238.1)	(34.9)	Mean (mg. %)	(217.3)	(38.9)	Mean (mg. %)	(218.4)	(53.2)

Four blood samples were analyzed from each man on each of two diets in each experiment. The absolute grand means, in mg. per 100 ml., are given in parentheses at the end of each column.

However, the agreement between observation and prediction is not quite this good. On the average, the patients of Farquhar and Sokolow seem to be intrinsically somewhat hypercholesteremic, so the predicted Δ Chol. should allow for this fact. Accordingly, the best prediction for Δ Chol. would be somewhat greater than – 59, more like – 70 mg. per 100 ml. Alternatively, it could be suggested that their patients did not precisely exchange 30.8 per cent of control diet fat calories for safflower oil. If it is presumed that they faithfully ingested the safflower oil daily in an amount calculated to represent about 31 per cent of their calory requirements, it is questionable whether the corresponding reduction in their control diet was achieved entirely at the expense of control diet fat. For example, if they were no longer allowed to have butter, did they actually continue to eat the same amount of bread as before An average reduction of only a slice or two of bread daily during the safflower oil period would account for the discrepancy between observation and prediction.

Ahrens et al.[12] provided adequate dietary data for their experiments with formula feeding but their material is peculiar in several regards: 1.

TABLE 10.—*Estimates of the Intercept, a, and the Slope, b, in Equation 4: $\Delta\% = a + bX\%$, where $X\%$ is the Individual Serum Cholesterol Value as % of the Group Mean on a Reference Diet, and $\Delta\%$ is the Predicted Change of the Same Person as % of the Group Mean Change*

Series	N	Ref. Chol. (mg. %) Mean	±	S.D.	Δ Chol. (mg. %) Mean	±	S.D.	a	$b \pm SE_b$
Hatch et al.[8]	24	222.1	±	34.0	34.6	±	34.8	–180	2.80±0.74
Best et al.[9]	14	312.1	±	188.0	53.0	±	55.4	–110	2.10±0.22
Farquhar and Sokolow[10]	15	232.7	±	41.7	48.7	±	22.5	– 69	1.69±0.56
N series, H to SO	24	207.3	±	25.4	48.2	±	19.9	– 73	1.73±0.25
N series, H to CO	24	207.3	±	25.4	46.7	±	19.2	– 64	1.64±0.24
Expt. V	18	238.1	±	44.9	34.9	±	15.6	– 92	1.92±0.39
Expt. VII	24	217.3	±	34.4	38.9	±	18.2	– 93	1.93±0.58
Expt. IX	26	218.4	±	35.5	53.2	±	21.4	– 59	1.59±0.28
Weighted mean	169	226.7		—	44.5		—	– 91	1.91 —

Group means (and standard deviations) are in absolute terms (mg. %).
N, number of persons.

They used no ordinary diets but only liquid formulas. 2. Individual patients were studied repeatedly but it is not possible to analyze group averages so as to reduce the factor of individual variation. 3. Most of their patients were metabolically abnormal, as indicated by hypercholesteremia, xanthomatosis, etc. Two patients (nos. 13 and 15), who suffered from arteriosclerotic heart disease and myocardial infarction as well as xanthomatosis and hypercholesteremia, were remarkable in being almost completely uninfluenced by the diet.

However, it is of interest to consider the predictions for the results of changes in the fats in the formula diet. Figure 1 includes all of the data on the men studied by Ahrens et al. with the exception of comparisons involving coconut oil. The latter were omitted because of our suspicion that the short-chain fatty acids in coconut oil have a rather different quantitative effect from the fatty acids in most common food fats.[2] The mean chain length in coconut oil is only 12.4 compared with 15.0 for butter and 16 to 17.5 for most other food fats and oils. The predicted values in figure 1 were obtained by the application of equations 4D and 2E. The coefficient of correlation between predicted and observed values is $r = + 0.94$. If the 3 values from patient no. 15 are omitted, the coefficient of correlation, between the observed cholesterol change in response to diet change and that predicted, is $r = + 0.955$. Their patient no. 1, who had the most extreme hypercholesteremia, makes a large contribution to the correlation coefficient, but even when he is omitted the correlation between observed and predicted Δ Chol. is $r = 0.86$.

For comparison with figure 1, we have used equations 2E and 4D to predict the individual cholesterol responses of our subjects in changing from the H to the SO diet in experiment N. The result is given in figure 2. The correlation between observed and predicted cholesterol values of the individual men on the SO diet is $r = 0.85$. It should be observed, of course, that intraindividual variability in serum cholesterol, plus the error of the method of measurement, means that any single estimate of cholesterol change is subject to an appreciable error. Accordingly, in a sample of subjects who exhibited only a limited range of intrinsic differences, it cannot be expected that an extremely high correlation will be found between observed and predicted values.

DISCUSSION

The variations in total serum cholesterol concentration considered here are the result of variations in the cholesterol in the beta lipoprotein fraction as separated by paper electrophoresis or by cold ethanol fractionation. The alpha lipoprotein cholesterol is not altered by changes in the fat in the diet and, for that matter, no dietary manipulation is known to affect the level of the alpha fraction. Farquhar and Sokolow[10] found the average serum concentration of alpha lipoprotein cholesterol to be the same in their subjects on their control diet, on their safflower oil diet, and during the periods of sitosterol administration. Similar constancy of the alpha fraction was found in all of our experiments with different amounts and kinds of fats in the diet, as well as in our comparisons of populations habitually subsisting on different diets.[5, 13, 14]

TABLE 11.—*Observed and Predicted Mean Serum Cholesterol Values, Mg. per 100 Ml., in 4 Experiments*

Item	Expt. I	Expt. II	Expt. VII	Expt. VIII
1. Diet 1, type	Corn oil	Milk fat	Olive oil	Rape seed oil
2. Diet 1, % cal. from saturated fats	6	23	5	3
3. Diet 1, % cal. from polyunsaturated fats	21*	3*	5*	11*
4. Diet 1, cholesterol, observed	140	190	185	170
5. Diet 1, cholesterol, predicted for reference men†	165	233	182	180
6. Diet 2, type	Milk fat	Corn oil	Corn oil	Corn oil
7. Diet 2, % cal. from saturated fats	23	6	6	6
8. Diet 2, % cal. from polyunsaturated fats	3*	21*	21*	21*
9. Diet 2, cholesterol observed	175	140	170	158
10. Δ cholesterol observed	+35	−50	−15	−12
11. Δ cholesterol predicted†	+47	−54	− 8	−12

Data from Malmros and Wigand[11] on 12 subjects in experiments I and II, 11 subjects in experiments VII and VIII. Diet periods 4 weeks each in experiments I and II, 2½ weeks in the first period and 1 week in the second in experiments VII and VIII.

*Including estimate of 1% of total calories from linoleic acid in cereals and vegetables in the diet.

†Men who average 225 mg. % on diet with S=20%, P=3%. For such men, Chol. −225= 2.68 (S-20) −1.23 (P-3).

The present analysis is concerned entirely with adult men. We have conducted no experiments with women or children. There is no information in the literature which proves that cholesterol responses to the diet are identical in the 2 sexes but if they are not, they are similar, at least, to judge from the experimental data of Groen et al.,[15] Ahrens et al.,[12] and Malmros and Wigand.[11] Surveys of both sexes in populations subsisting habitually on different diets also indicate that men and women are much alike in their cholesterol response to the diet.[16]

The surveys of Scrimshaw, Balsam and Arroyave[16] suggest that the general cholesterol response of children to fats in the diet is similar to that of adults. It is clear that children[17] are like adult men in being uninfluenced by large variations in dietary cholesterol.[18] However, though we suspect that the relative effects on the serum cholesterol of different types of fatty acids in the diet are the same in children and in adults, the available data do not make it possible to decide whether the absolute effect is the same. It cannot be stated, for example, that intrinsic serum cholesterol level in a child bears the same relationship to serum cholesterol responsiveness as found among adults.

The present analysis is concerned with the isocaloric exchange of fats for other fats or for carbohydrates in the diet. What may happen when a fat *supplement* is added to the diet is conjectural in the absence of other information. If the body weight remains constant in spite of such supplementation, this means that either the calories spent for physical activity have been increased or that the basic diet has been reduced in an amount to correspond with the calories in the supplement. The latter would seem to be more likely in most cases and the question then is as to the particular kinds of foods reduced in the basic diet.

We presume that, in general, the ingestion of a fat supplement will tend to decrease the appetite for fat and that, in effect, the prescription of a fat supplement such as corn or safflower oil may automatically bring about some degree of substitution for other fat in the basic diet. The "other fats" would be, of course, those most easily altered in the diet of the patient by his spontaneous choice, i.e., the saturated fats of butter and of meats. Unless allowance were made for the possibility of such spontaneous substitution, it would be

erroneous to credit a cholesterol response solely to the effect of the fat supplement.

We have discussed this point in connection with our experiments with supplements of different kinds of fats for medical students who were instructed to continue with their ordinary diet while taking the supplements.[19] That some substitutions did occur was shown by the fact that the students did not gain enough weight to correspond with the extra calories in the supplements.

The recent report of Perkins, Wright, and Gatje[20] is of interest in this connection. Their 24 male medical students received, alternately, an emulsion providing 48 Gm. safflower oil daily or a carbohydrate "placebo" providing 240 calories. The safflower oil preparation, which also contained a mixture of 5 emulsifying (surface active) agents, supplied 450 calories. During the period on the supplement there was an average weight gain of 2 Kg. but it is not clear whether this refers only to the 6 to 7 weeks on the safflower oil supplement or to the entire 13 weeks on the oil or placebo supplements. In any case, the weight gain is less than would correspond to the excess calories provided in the supplement, an excess which adds up to about 21,000 calories during the oil period and 11,000 during the placebo. In terms of adipose tissue these calories correspond to about 3 Kg. for the oil period and close to 5 Kg. for the entire 13 weeks. We conclude therefore that the basic diet must have been reduced or that these young men increased their physical activity by about 200 calories daily.

Perkins et al. stated that the average basic diet (estimated by questionnaire) before the start of the study provided 2,350 calories daily. The usual composition of safflower oil being assumed, with about 12 per cent saturated and 78 per cent polyunsaturated fatty acids, this means that the 48 Gm. oil supplement provided a daily average of about 5.8 Gm. saturated and 37.4 Gm. polyunsaturated fatty-acid glycerides. The basic diet, of the usual American type, provided 42 per cent of total calories from fats, so it may be estimated as being characterized as $S_1 = 21$ and $P_1 = 3$ (per cent of calories from glycerides of saturated and poly-unsaturated fatty acids). During the oil supplementation, the basic diet was *not* actually decreased, the diet would have been $S_2 = 19.5$ and $P_2 = 14.5$.

From equation 2C the average expected cholesterol change would be then Δ Chol. = 2.68 (19.5-21.0) − 1.23 (14.5-3.0) = −18.1 mg. per 100 ml. However, these young men are, compared with our reference, intrinsically hypocholesteremic, with an average of 191.5 mg. cholesterol per 100 ml. on the control diet, while the reference men would have an average of 229.5 on that diet. Correcting for this fact (by applying equation 4D), the predicted result of the oil supplement on the cholesterol level of these young men is an average fall of 15.1 mg. per 100 ml. Actually, in *both* safflower oil and placebo periods the serum cholesterol steadily rose, and after 13 weeks the average was an increase of 22 mg. for the 12 men ending with the placebo and of 29 mg. for the 12 who had the oil emulsion during the final 6 weeks.

Consideration of the experiment of Perkins, Wright, and Gatje leads to the conclusion that only a small effect of the safflower oil emulsion could have been expected and that other factors, probably including changes in the basic diets, were operative during the period of the experiment. The latter conclusion is also in accord with the expectation that freely selected diets will necessarily change from late summer (the control period) to early winter.

Summary

The effects on serum cholesterol concentration of different percentages of total calories supplied by glycerides of saturated (S), monoene (M) and polyunsaturated (P) fatty acids were analyzed in terms of the prediction equation

$$Chol._2 - Chol._1 = b(S_2 - S_1) + c(M_2 - M_1) + d(P_2 - P_1)$$

where Chol. is in mg. per cent and the subscripts refer to first and second diets.

The coefficients in this equation obtained by the method of least squares from the data of

19 sets of dietary comparisons, with 12 to 22 men in each set, were not different with statistical significance from those obtained in a previous analysis of 41 sets of similar data. The final result from the combined analysis of all 60 sets of comparisons was b = 2.68 ± 0.08, c = 0, d = −1.23 ± 0.07.

These coefficients apply to the average Δ Chol. of reference men in calory equilibrium who have an average of about 225 mg. cholesterol per 100 ml. of serum on a diet in which the values of S and P, as percentages of total calories, are about 20 and 3, respectively.

Men who are intrinsically hypercholeremic exhibit greater cholesterol response to dietary changes, while hypocholesteremic men are less responsive than reference men. In general, if X% is the cholesterol value of an individual, expressed as percentage of the average of a group of men on the same diet, and Δ% is that individual's cholesterol response in changing to another diet, also expressed as percentage of the group average response to the same dietary change, we have

$$\Delta\% = 1.91\ X\% - 91.$$

Analyses of 9 sets of data (5 original and 4 from the literature) yielded coefficients not significantly different from those in the above equation.

Published data from controlled dietary experiments in Sweden and in New York show serum cholesterol changes resulting from given dietary changes that are highly correlated with the results predicted from calculations based on the equations and coefficients given in the foregoing.

It is concluded that in man (a) oleic acid glyceride in the diet is substantially the equivalent, in serum cholesterol effect, of equal calories from carbohydrate, (b) the glycerides of saturated fatty acids in ordinary food fats raise the serum cholesterol level, those of poly-unsaturated fatty acids (mainly linoleic acid) lower it, and in this respect it requires slightly more than 2 Gm. of linoleic acid to counter the effect of 1 Gm. of a saturated fatty acid such as stearic or palmitic acid, (c) intrinsic relative hypercholesteremia is generally associated with relative hyper-responsiveness to dietary fat changes, and (d) the above relationships allow reasonably accurate predictions of group average responses in serum cholesterol level to given changes in dietary fats.

Acknowledgment

We are grateful to Drs. L. W. Beck, F. H. Mattson, and P. W. Ifland of the Procter and Gamble Company, Miami Valley Laboratories, for detailed analyses of dietary fats. Mrs. Helen Williams supervised the dietary management of the subjects and, with Mrs. Nedra Foster, was responsible for most of the practical features of dietary planning. Mrs. Foster also had a major responsibility in the cholesterol analyses performed by herself and Dr. Paul Kupchs, Mrs. Rose Marie Keidel, and Mrs. Susanna Van Wyk. Mrs. Olive Herder and Mrs. Mary Jane Schweich assisted in the collection and analysis of diets and in the computation of nutrient intake. Volunteers from the Brethren Service Committee gave devoted, unceasing, and intelligent service in the maintenance of the subjects and their diets: Roger Dean, Norman Reeder, Gale Honeyman, Russell Vermillion, James Harlow, Robert Du Vall, Charles Barton, and Gerald Rhodes.

Summario in Interlingua

Le effectos producite in le concentration de cholesterol del sero per suppler le calorias total in le forma de varie proportiones de glyceridos de acidos grasse saturate (S), monoenic (M), e poly-nonsaturate (P) esseva analysate super le base del equation de prediction:

$$Chol._2 - Chol._1 = b(S_2 - S_1) + c(M_2 - M_1) + d(P_2 - P_1)$$

in que Chol representa cholesterol in mg pro cento e in que le cifras abassate se refere a un prime e secunde dieta.

Le coefficientes obtenite per iste equation secundo le methodo de quadratos minime ab le datos de 19 experimentos de comparation dietari, con inter 12 e 22 homines participante in cata un del experimentos, non differeva a grados de signification statistic ab le coefficientes correspondente que esseva obtenite previemente in 41 experimentos de natura similar. Le resultato final ab le analyse combinate de omne le 60 comparationes esseva b = 2,68 ± 0,08, c = 0, d = −1,23 ± 0,07.

Iste coefficientes es applicabile al valor medie de Δ Chol de subjectos de referentia in equilibrio caloric qui ha un valor medie de circa 225 mg de cholesterol per 100 ml de sero e un dieta in que le valores de S e P, como procentage del calorias total, es circa 20 e 3, respectivemente.

Homines qui es intrinsecamente hypercholesterolemic exhibi plus pronunciate responsas cholesterolic a alterationes dietari, durante que homines hypocholesterolemic es minus responsive que homines de referentia. In general, si X% es le valor de cholesterol in un certe individuo, exprimite como procentage del valor medie de un gruppo de homines con le mesme dieta, e si Δ% es le responsa cholesterolic del mesme individuo como effecto del transition a un altere dieta, etiam exprimite como procentage del valor medie del responsas de un gruppo al mesme alteration dietari, nos obtene:

$$\Delta\% = 1.91\ X\% - 91.$$

Le analyse de 9 series de datos, 5 original e 4 ab le litteratura, resultava in coefficientes non significativemente differente ab illos in le supra-presentate equation.

Datos in le litteratura, ab controlate experimentos dietari effectuate in Sveda e in New York, monstra alterationes del cholesterol del sero in consequentia de specific alterationes dietari que es correlationate a alte grados con le resultatos predicite per calculationes super le base del equationes e coefficientes supra-presentate.

Es concludite que in humanos (a) glyceride de acido oleic in le dieta es essentialmente le equivalente, quanto al effecto super le cholesterol del sero, de carbohydrato con le mesme valor caloric, (b) le glyceridos de saturate acidos grasse in ordinari grassias alimentari augmenta le nivello de cholesterol in le sero, illos de poly-nonsaturate acidos grasse (principalmente acido linoleic) reduce lo, e in iste respecto levemente plus que 2 g de acido linoleic es requirite pro contrariar le effecto de 1 g de saturate acido grasse como per exemplo acid stearic o palmitic, (c) intrinsec hypercholesterolemia relative es generalmente associate con hyper-responsivitate relative a alterationes de grassia dietari, e (d) le relationes hic discutite permitte satis accurate predictiones del responsas medie del nivello de cholesterol del sero in gruppos de individuos como effecto de specific alterationes del grassias dietari.

REFERENCES

1. Keys, A., Anderson, J. T., and Grande, F.: Serum-cholesterol response to dietary fat. Lancet **1**: 787, 1957.
2. —, —, and —: Prediction of serum cholesterol responses of man to changes of fats in the diet. Lancet **2**: 959, 1957.
3. Grande, F., Anderson, J. T., and Keys, A.: Serum cholesterol in man and the unsaponifiable fraction of corn oil in the diet. Proc. Soc. Exper. Biol. & Med. **98**: 436, 1958.
4. Keys, A., Anderson, J. T., and Grande, F.: The effect on serum cholesterol in man of mono-ene fatty acid (oleic acid) in the diet. Proc. Soc. Exper. Biol. & Med. **98**: 387, 1958.
5. Anderson, J. T., Keys, A., and Grande, F.: The effects of different food fats on serum cholesterol concentration in man. J. Nutrition **62**: 421, 1957.
6. —, and —: Cholesterol in serum and lipoprotein fractions, its measurement and stability. Clin. Chem. **2**: 145, 1956.
7. Starke, H.: Effect of the rice diet on the serum cholesterol fractions of 154 patients with hypertensive vascular disease. Am. J. Med. **9**: 494, 1950.
8. Hatch, F. T., Abell, L. L., and Kendall, F. E.: Effects of restriction of dietary fat and cholesterol upon serum lipids and lipoproteins in patients with hypertension. Am. J. Med. **19**: 48, 1955.
9. Best, M. M., Duncan, C. H., Van Loon, E. J., and Wathen, J. D.: The effects of sitosterol on serum lipids. Am. J. Med. **19**: 61, 1955.
10. Farquhar, J. W., and Sokolow, M.: Response of serum lipids and lipoproteins of man to beta-sitosterol and safflower oil. Circulation **17**: 890, 1958.
11. Malmros, H., and Wigand, G.: The effect on serum-cholesterol of diets containing different fats. Lancet **2**: 1, 1957.
12. Ahrens, E. H., Jr., Hirsch, J., Insull, W., Jr., Tsaltas, T. T., Blomstrand, R., and Peterson, M. L.: The influence of dietary fats on serum-lipid levels in man. Lancet **1**: 943, 1957.

13. Keys, A.: Diet and the epidemiology of coronary heart disease. J.A.M.A. **164**: 1912, 1957.
14. —, Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larsen, N. P., and Keys, M. H.: Lessons from serum cholesterol studies in Japan, Hawaii and Los Angeles. Ann. Int. Med. **48**: 83, 1958.
15. Groen, J., Tjiong, B. K., and Kamminga, C. E.: The influence of nutrition, individually and some other factors, including various forms of stress, on the serum cholesterol; an experiment of nine months' duration in 60 normal human volunteers. Voeding **13**: 556, 1952.
16. Scrimshaw, N. S., Balsam, A., and Arroyave, G.: Serum cholesterol levels in school children from three socio-economic groups. Am. J. Clin. Nutrition **5**: 629, 1957.
17. Heymann, W., and Rack, F.: Independence of serum cholesterol from exogenous cholesterol in infants and in children. Am. J. Dis. Child. **65**: 235, 1943.
18. Keys, A., Anderson, J. T., Mickelsen, O., Adelson, S. F., and Fidanza, F.: Diet and the serum cholesterol in man: Lack of effect of dietary cholesterol. J. Nutrition **59**: 39, 1956.
19. Armstrong, W. D., Van Pilsum, J., Keys A., Grande, F., Anderson, J. T., and Tobian, L.: Alteration of serum cholesterol by dietary fats. Proc. Soc. Exper. Biol. & Med. **96**: 302, 1957.
20. Perkins, R., Wright, I. S., and Gatje, B. W.: Effect of safflower oil emulsion on serum cholesterol levels in young adult males. J.A.M.A. **166**: 2132, 1958.

Medical Eponyms

By Robert W. Buck, M.D.

Aschoff Bodies. These structures were first described by Ludwig Aschoff (1866-1936), then Professor of Pathology at Freiburg, in an article entitled "The Problem of Myocarditis" ("Zur Myocarditisfrage") which may be found in the *Verhandlungen der Deutschen Pathologischen Gesellschaft*, Achte Tagung, Jahrgang 1904, Heft 2, Jena, 1905, pp. 46-53.

"We succeeded in finding peculiar nodules which seemed to be specific for rheumatic myocarditis. These nodules were clearly marked, it is true, in only two cases of recurrent endocarditis, but corresponded in their location exactly to the cellular proliferation found in other cases. They usually lay in the neighborhood of small or medium sized blood vessels and often showed the most intimate relation to the adventitia of these vessels, or there was found simultaneous involvement of all layers of the blood vessels, such as has been described in arteriitis nodosa. The nodules are extremely small, at most submiliary in size, and arise through the collection of notably larger elements with one or more abnormally large, slightly notched, or polymorphic nuclei. The aggregation of cells often occurs in the form of a fan or rosette. The periphery is formed by the large nuclei; the center by the confluent protoplasm of the cells which often seems to stain weakly, or otherwise appears to be a necrotic mass. The fan-shaped foci recall, when superficially observed, the tiny necrotic areas of gout with the peripheral cell mantle as they are frequently found in gouty kidneys."

Severe Acidosis and Hyperpotassemia Treated with Sodium Bicarbonate Infusion

By KUNO C. SCHWARZ, M.D., BURTON D. COHEN, M.D., GLENN D. LUBASH, M.D., AND ALBERT L. RUBIN, M.D.

Four uremic patients with severe acidosis, hyperpotassemia, and electrocardiographic signs of toxicity were treated with intravenous sodium bicarbonate. Serial determinations showed a fall in plasma potassium, a rise in blood pH, and regression of the electrocardiogram toward normal. The mechanisms responsible for these changes are discussed.

HYPERPOTASSEMIA is a serious and often fatal complication of advanced renal insufficiency. Its principal lethal action is its depressant effect on the myocardium.[1, 2]

In uremia, hyperpotassemia is frequently accompanied by acidosis, hyponatremia, hypocalcemia, alterations in body water, and changes in cellular metabolism.[3] Correction of these associated electrolyte abnormalities is often accompanied by improvement in the electrocardiographic manifestations of hyperpotassemia. In the correction of hyperpotassemia and acidosis with alkali salts, therapeutic success has been achieved with both sodium bicarbonate and sodium lactate. Recently, the latter agent has been the more popular. This report outlines our experience with 4 uremic patients with severe acidosis, hyperpotassemia, and electrocardiographic evidence of advanced cardiac effects. Treatment consisted of the rapid infusion of 5 per cent sodium bicarbonate and, in each case, correction of the acidosis was accompanied by lowering of plasma potassium and reversal of the electrocardiographic signs.

METHODS

Plasma sodium and potassium were determined on a Perkin-Elmer, Model 52-A flame photometer, with use of a lithium internal standard. Plasma chlorides were determined by the method of Schales and Schales, as modified by Summerson. Venous blood pH was determined on a Cambridge Research pH meter with use of a constant-temperature water bath to maintain at 37 C. Plasma volume was measured by the dye-dilution technic with T 1824.

CASE REPORTS

Case 1. B. R., a 46-year-old woman with polycystic kidney disease, was admitted to another hospital with symptoms of uremia. On admission, physical examination revealed masses in both flanks. The blood urea nitrogen was 90 mg. per cent. The plasma sodium was 134 mEq./L., plasma potassium 4.8 mEq./L., and plasma chloride 108 mEq./L. Carbon dioxide combining power was not determined. An electrocardiogram was within normal limits. Five days after admission the patient became disoriented, and deep respirations were noted. She was transferred to Bellevue Hospital for possible dialysis with the artificial kidney.

Plasma electrolyte values on admission were potassium 5.9 mEq./L., chloride 89 mEq./L., carbon dioxide combining power 1.3 mM/L., and blood pH 7.18. The blood urea nitrogen was 100 mg. per cent. Plasma volume was markedly reduced. The electrocardiogram revealed peaked T waves (fig. 1, 10:05 p.m.). Because of the severe symptomatic acidosis, an intravenous infusion of 5 per cent sodium bicarbonate was begun. After administration of 408 mM (34 Gm.) of sodium bicarbonate in 4 hours, the patient's respirations became normal and her sensorium cleared. An electrocardiogram at this time had changed and now suggested hypopotassemia. The duration of the QRS complex was now normal (fig. 1, 2:00 a.m.). The plasma electrolyte values were sodium 144 mEq./L., potassium 3.0 mEq./L., chloride 89 mEq./L., and carbon dioxide combining power 6.2 mM/L. The blood pH was 7.29. During this interval urinary output was 200 ml. with electrolyte concentrations of sodium 87.0 mEq./L., potassium 31.0 mEq./L., and chloride 38.0 mEq./L.

Subsequently the patient was maintained on 5 to 10 Gm. of sodium bicarbonate a day during

From the Cardio-Renal Laboratory of the Second (Cornell) Medical Division, Bellevue Hospital, and the Department of Medicine, Cornell University Medical College, New York, N.Y.

This work was supported in part by grants from the New York Heart Association and the U.S. Public Health Service (H-2054C).

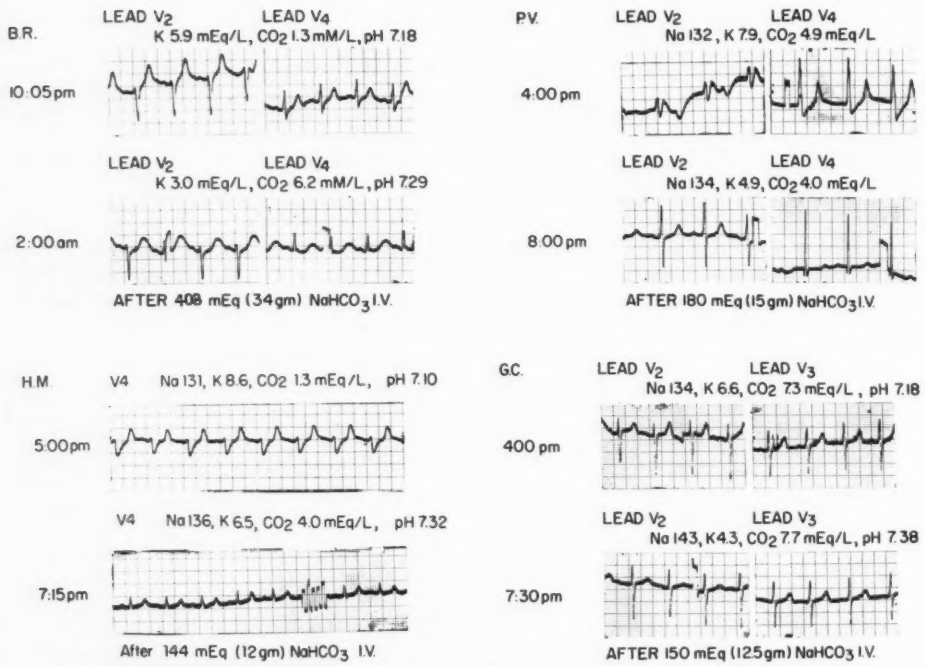


FIG. 1 *Top left.* Electrocardiogram before and after the administration of sodium bicarbonate. Note the alterations suggestive of hypopotassemia at 2:00 a.m.

FIG. 2 *Bottom left.* Electrocardiogram before and after the administration of sodium bicarbonate showing regression of conduction disturbances and return of sinoatrial activity.

FIG. 3 *Top right.* Electrocardiogram before and after the administration of sodium bicarbonate showing regression of conduction disturbance, lowering of the T waves and return of sinoatrial activity.

FIG. 4 *Bottom right.* Electrocardiogram before and after the administration of sodium bicarbonate suggesting lowering of peaked T waves.

hospitalization. This amount of sodium bicarbonate was found necessary to maintain the carbon dioxide combining power between 15 and 20 mM/L. She was accordingly discharged on maintenance bicarbonate therapy.

Case 2. H. M., a 28-year-old white woman, was admitted to a local hospital with acute renal failure associated with a *Bacillus Welchii* infection following an induced abortion. She was oliguric for 8 days and was transferred to Bellevue Hospital for dialysis with the artificial kidney. On admission the blood pressure was 90/60 and the respirations were deep. Chvostek and Trousseau signs were present. The electrocardiogram showed prolongation of the QRS complex and atrial arrest (fig. 2, 5:00 p.m.). Plasma electrolyte values were sodium 131 mEq./L., potassium 8.6 mEq./L., chloride 90 mEq./L., carbon dioxide combining power 1.3 mM/L., and calcium 5.4 mg. per cent. Blood pH was 7.10 and urea nitrogen was 210 mg. per cent. Plasma volume was within normal limits.

While preparations for dialysis were being made, 144 mM (12 Gm.) of sodium bicarbonate and 2 Gm. of calcium gluconate were administered intravenously in 2 hours and 15 minutes and, at the start of dialysis, the electrocardiogram revealed normal sinus rhythm with normal intraventricular conduction (fig. 2, 7:15 p.m.). At this time, plasma sodium was 136 mEq./L., potassium 6.5 mEq./L., carbon dioxide combining power 4.0 mM/L., the blood pH was 7.32. Urinary output was negligible. The patient did not improve and died 24 hours after dialysis.

Case 3. P. V., an 89-year-old white woman, was admitted to the urologic service because of 2 weeks of dysuria. Two days prior to admission she developed hematuria, suprapubic pain, and malaise. On admission, she appeared cachectic and dehy-

drated. Blood pressure was 170/60 and respirations were deep and regular at a rate of 24 per minute.

Initially the patient was oliguric, with a urinary output of less than 10 ml. per hour, and urinalysis revealed a specific gravity of 1.020, 2 plus albumin, a trace of acetone, and many red blood cells. The hematocrit level was 27 per cent. The plasma electrolyte values were sodium 137 mEq./L., potassium 8.3 mEq./L., chloride 112 mEq./L., and carbon dioxide combining power 6.3 mM/L. The blood urea nitrogen was 164 mg. per cent.

Because of the dehydration and oliguria she was given 3,000 ml. of 5 per cent dextrose in water in the first 12 hours, during which time she remained oliguric. Her neck veins became distended and a venous pressure was 180 mm. of saline, at which time she was seen by a medical consultant. Plasma volume was expanded by approximately one liter over the mean predicted value. The red cell mass was decreased, and the hematocrit level was 18 per cent. Electrocardiogram showed peaking of the T waves, prolongation of the QRS complex, and atrial arrest (fig. 3, 4:00 p.m.). The plasma electrolyte values were sodium 132 mEq./L., potassium 7.9 mEq./L., and carbon dioxide combining power 4.9 mM/L. At this time the blood pressure became unobtainable.

In view of the abnormal electrocardiogram, the appearance of shock, and the persistent, severe, symptomatic acidosis, an intravenous infusion of 5 per cent sodium bicarbonate was begun. After administration of 180 mM (15 Gm.) of sodium bicarbonate in 4 hours followed by 1 unit of whole blood, the electrocardiogram revealed normal sinus rhythm, lowering of the T waves, and normal intraventricular conduction (fig. 3, 8:00 p.m.). The plasma electrolytes were sodium 134 mEq./L., potassium 4.9 mEq./L., chloride 111 mEq./L., and carbon dioxide combining power 4.0 mM/L. During this interval, respirations became normal, the arm venous pressure fell to 110 mm. saline and the blood pressure rose to 110/70. Throughout the succeeding 24 hours she received an additional 150 mEq. (12.5 Gm.) of sodium bicarbonate and the plasma carbon dioxide combining power rose to 10.8 mM/L. Oliguria persisted, and cystoscopy revealed severe, generalized, pseudomembranous cystitis obscuring both ureteral orifices. Culture of the urine showed *Bacillus proteus*, and the patient was treated with tetracycline. During this period urinary volumes increased to 1,000 ml. daily. Subsequently, the patient developed high, spiking fever and hypotension and died on the eighth hospital day. Postmortem examination revealed chronic pyelonephritis with contracted kidney, severe hemorrhagic cystitis, partial ureteral obstruction bilaterally, and hydronephrosis.

Case 4. G. C., a 19-year-old white girl with chronic glomerulonephritis, was admitted to the hospital because of oliguria. She was comatose and respirations were deep and labored. Electrocardiogram revealed normal sinus rhythm and suggested peaking of the T waves (fig. 4, 4:00 p.m.). Plasma electrolyte values were sodium 134 mEq./L., potassium 6.6 mEq./L., chloride 109 mEq./L., carbon dioxide combining power 7.3 mM/L.; the blood pH was 7.18. The blood urea nitrogen was 102 mg. per cent. Plasma volume was normal.

An intravenous infusion of 5 per cent sodium bicarbonate was begun. After 150 mM (12.5 Gm.) had been administered in 3½ hours, the electrocardiogram showed slight decrease in the height of the T waves (fig. 4, 7:30 p.m.). Plasma electrolyte values were sodium 143 mEq./L., potassium 4.3 mEq./L., chloride 105 mEq./L., carbon dioxide combining power 7.7 mM/L., and blood pH 7.38. Respirations became normal but there was no other change in clinical status. The following day, after an additional 108 mM (9.0 Gm.) of sodium bicarbonate intravenously, the plasma carbon dioxide combining power rose to 11.2 mM/L. Subsequently, urinary volumes increased to between 700 and 1,000 ml. daily, and the patient improved markedly over a 2-week period.

Discussion

The serial electrocardiographic changes in potassium intoxication are well known.[4] The relatively poor correlation of these changes with the plasma level of potassium[5, 6] probably reflects the role of ions other than potassium as well as the complex shifts in intracellular-extracellular ion concentrations that occur in the presence of altered states of hydration, acid-base balance, and cellular metabolism.[7]

In uremia only a few of the factors contributing to potassium metabolism and cardiac toxicity can be defined. These include metabolic acidosis, hyponatremia, hypocalcemia, dehydration, and increased catabolism.

Animal experiments have shown an inverse relationship between blood pH and plasma potassium concentration.[8] It has been demonstrated in dogs that perfusion with acidic solutions produces electrocardiographic changes analogous to those produced during infusion with potassium.[9–11] Rise in plasma potassium was demonstrated uniformly throughout the induction of acidosis, but cardiac toxicity was manifest at lower levels of

hyperpotassemia. This potentiation of potassium toxicity by acidosis has also been suggested by studies in patients with diabetic acidosis.[12]

Hyponatremia may augment the changes produced by an increase in plasma potassium.[13] Metabolic acidosis is often associated with increased renal sodium excretion. In addition, increased quantities of sodium may enter the cell to buffer the fall in intracellular pH. Together, these may lead to a fall in plasma sodium concentration. Finally, studies on isolated cardiac muscle as well as in intact animals and human subjects have shown that hypocalcemia, also, potentiates the effect of hyperpotassemia.[14–16]

Dehydration, increased catabolism, and hypotension, all of which may accompany uremia, cannot be so clearly related to cardiac toxicity. With sustained increased catabolism, as in fever with infections, hyperpotassemia may occur. Hypotension frequently leads to myocardial ischemia; increased sensitivity to potassium has been demonstrated in hypoxic states.[17]

Hyperpotassemia constitutes a serious medical emergency. Its management includes hemodialysis, cation exchange resins, intravenous infusion of hypertonic glucose and insulin, hypertonic saline, calcium salts and, most recently, molar sodium lactate.[18, 19]

These agents fall into 2 major groups. The first, which includes dialysis, resins, and glucose infusions, acts through the direct removal of potassium from the extracellular fluid. The second group, comprising hypertonic saline and calcium infusions, may also encourage intracellular transfer of potassium, but produces an additional effect through replacement of ions, deficiency of which potentiates hyperpotassemia.

Recent reports have appeared on the use of molar sodium lactate in the treatment of advanced cardiac toxicity due to hyperpotassemia, with prompt reversal of electrocardiographic changes and rapid clinical improvement.[18, 19] The authors suggest the possibility of a specific action of lactate ion in addition to the effect of this therapy on acidosis, extracellular fluid volume, and intracellular potassium shifts.

Our observations indicate that correction of the bicarbonate deficit with sodium bicarbonate lowers plasma potassium directly, apparently through intracellular transfer of potassium ions. We were led to employ 5 per cent sodium bicarbonate because of the severe clinical acidosis that the 4 patients presented in addition to the electrocardiographic signs of hyperpotassemia. Treatment of acidosis in this manner reversed the electrocardiographic signs. These effects were identical to those reported by Bellet[18, 19] with the use of sodium lactate.

In each instance, plasma potassium was lowered. Since urinary potassium excretion was negligible during the period of infusion, it may be assumed that this was accomplished in large measure through intracellular transfer, although expansion of normal extracellular volume may have played a small role. In addition, blood pH rose in the 3 instances in which values were obtained. The plasma carbon dioxide combining power changed only slightly immediately following the bicarbonate infusion. The administration of additional sodium was probably not important, since initial plasma values were only slightly reduced. The results of treatment were similar whether or not there was a significant alteration in plasma sodium. The effect of bicarbonate infusion appears to be independent of correction of dehydration, since the initial plasma volume was not reduced in 3 of the 4 patients.

The mechanism by which sodium bicarbonate acts in this instance seems to depend, therefore, upon its effectiveness in reducing the plasma concentration of potassium ions, and possibly hydrogen ions. The latter is accomplished directly by means of repletion of buffer alkali, and is best demonstrated by serial pH determinations. Moreover, correction of extracellular alkali deficit is accompanied by restoration of intracellular bicarbonate as well. Since potassium is the major intracellular cation, correction of intracellular acidosis is associated with a shift of po-

assium as well as bicarbonate into the cell, nd hence a reduction in plasma potassium oncentration.

Summary

In 4 uremic patients with severe clinical cidosis associated with electrocardiographic vidence of hyperpotassemia, intravenous administration of 5 per cent sodium bicarbonate esulted in correction of the acidosis, fall in plasma potassium, and reversal of electrocardiographic signs. The effect of this treatment did not depend on changes in plasma sodium, renal excretion of potassium, or on correction of dehydration.

In the treatment of severe acidosis, reversal of electrocardiographic signs of hyperpotassemia parallels more closely the correction of blood pH than it does alteration in plasma carbon dioxide combining power. The results suggest that the infusion of hypertonic sodium bicarbonate in patients with hyperpotassemia, acidosis, and electrocardiographic signs of cardiac toxicity has proved a safe and practical measure in the emergency management of this common problem in the uremic syndrome.

Acknowledgment

We are indebted to Mrs. Ruth Aronson and Miss Carolyn Register for their technical assistance.

Summario in Interlingua

In 4 patientes uremic con sever acidosis linic, associate con signos electrocardiographic de hyperkalemia, le administration intravenose de bicarbonato de natrium de 5 ro cento resultava in le correction del acidosis, un reduction del kalium del plasma, e un eversion del signos electrocardiographic. Le ffecto de iste tractamento non dependeva de lterationes in le natrium del plasma o in le xcretion renal o del correction del dishydration.

In le tractamento de sever acidosis, le reersion del signos electrocardiographic de yperkalemia es plus strictemente correlatinate con le correction del pH del sanguine ue con alterationes in le potentia del plasma de combinar dioxydo de carbon. Le resultatos suggere que le infusion de hypertonic bicarbonato de natrium in patientes con hyperkalemia, acidosis, e signos electrocardiographic de toxicitate cardiac es un practic e salve mesura de urgentia.

REFERENCES

1. Levine, H. D., Merrill, J. P., and Somerville, W.: Advanced disturbances in cardiac mechanisms in potassium poisoning. Circulation **3**: 889, 1951.
2. Marchand, J. D., and Finch, C. A.: Fatal spontaneous potassium intoxication in patients with uremia. Arch. Int. Med. **73**: 384, 1944.
3. Swann, R. C., and Merrill, J. P.: The clinical course of acute renal failure. Medicine **32**: 215, 1953.
4. Bellet, S.: The electrocardiogram in electrolyte imbalance. Arch. Int. Med. **96**: 618, 1955.
5. Tarail, R.: Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. Am. J. Med. **5**: 828, 1948.
6. Levine, H. D., and Relman, A. S.: The electrocardiogram in potassium depletion: Its relation to the total potassium deficit and the serum concentration. Am. J. Med. **16**: 395, 1954.
7. Dreifus, L. S., and Pink, A.: A clinical correlation study of the electrocardiogram in electrolyte imbalance. Circulation **14**: 815, 1956.
8. Abrams, W. B., Lewis, D. W., and Bellet, S.: The effect of acidosis and alkalosis on plasma potassium concentration and the electrocardiogram of normal and potassium depleted dogs. Am. J. M. Sc. **222**: 506, 1951.
9. Roberts, K. E., and Magida, M. G.: Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate and sodium as compared with those produced by an increase in potassium. Circulation **1**: 206, 1953.
10. Magida, M. G., and Roberts, K. E.: Electrocardiographic alterations produced by an increase in plasma pH, bicarbonate and sodium as compared with those seen with a decrease in potassium. Circulation Res. **1**: 214, 1953.
11. Surawicz, B., Braun, H. A., Crum, W. B., Kemp, R. L., Wagner, S., and Bellet, S.: Quantitative analysis of the electrocardiographic pattern of hypopotassemia. Circulation **5**: 750, 1957.

12. Nadler, C. S., Bellet, S., and Lanning, M.: Influence of serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. Am. J. Med. **5**: 838, 1948.
13. Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S., III: Clinical recognition and treatment of acute potassium intoxication. Ann. Int. Med. **33**: 797, 1950.
14. Hoffman, B. F., and Suckling, E. E.: Effect of several cations on the transmembrane potentials of cardiac muscle. Am. J. Physiol. **186**: 317, 1956.
15. Braun, H. A., Van Horne, R., Bettinger, C., and Bellet, S.: The influence of hypocalcemia induced by sodium ethylenediamine tetra acetate on the toxicity of potassium: An experimental study. J. Lab. & Clin. Med. **46**: 544, 1955.
16. Clark, M. E.: Action of calcium on the human electrocardiogram. Am. Heart J. **22** 367, 1941.
17. Bellet, S., Steiger, W. A., and Gazes, P. C.: The effect of different grades of myocardial infarction upon tolerance to potassium: An experimental study in dogs. Am. J. M. Sc. **220**: 247, 1950.
18. —, and Wasserman, F.: The effects of molar sodium lactate in reversing the cardiotoxic effect of hyperpotassemia. Arch. Int. Med. **100**: 565, 1957.
19. —, and —: Indications and contraindications for the use of molar sodium lactate. Circulation **15**: 591, 1957.

Berkowitz, D., Wagner, B. M., and Uricchio, J. F.: Acute Peptic Ulceration following Cardiac Surgery. Ann. Int. Med. **46**: 1015 (June), 1957.

Acute peptic ulceration following cardiac surgery has been demonstrated in 4 patients and clinically suspected in 3 others. This was a most serious complication, 4 of the patients having died. Another survived only after emergency gastric resection. Prompt diagnosis is essential for a favorable outcome and may be attained only by a constant alertness to the possibility of an acute ulcer in any postoperative cardiac patient who is not doing well. Early surgery rather than a more conservative program of therapy may be lifesaving in these patients and should not be withheld merely because the patient has recently undergone cardiac surgery. The exact mechanism responsible for an acute ulceration of the gastrointestinal tract following surgery is not well understood but it is believed that it represents a response to the alarm reaction described by Selye. Prolonged hypotension with resulting ischemia is an important factor in the pathogenesis and since many patients following cardiac surgery develop prolonged periods of hypotension, this particular complication is not altogether unexpected. It should be emphasized that this complication generally arises without any obvious background of peptic ulceration and without any prodromata. Melena, hematemesis, shock, or evidence of perforation may be the initial findings. In a group of patients who died following cardiac surgery from various causes, necropsy findings revealed an incidence of acute ulcerative lesions of the gastrointestinal tract of greater than 15 per cent.

Wendkos

Congenital Aneurysms of the Coronary Arteries with Report of a Case

By Ira Gore, M.D., John Smith, M.D., and Robert Clancy, M.D.

A case is presented of congenital aneurysm of a coronary artery in a patient with angina pectoris and myocardial infarction. Etiologies other than coronary atherosclerosis should be considered in young patients with clinical coronary disease; they include syphilitic ostial stenosis, coronary embolization, pulmonary origin of a coronary artery, and necrotizing arteritis in addition to aneurysm of a coronary artery. In this instance the aneurysm caused a shadow that was seen by x-ray but was not identified during life.

ISCHEMIC heart disease, currently one of the leading causes of disability and death, is largely a manifestation or complication of coronary atherosclerosis.[1] This is such a dominant relationship that other causes of coronary insufficiency are apt to be overlooked. Awareness of the clinical background, however, allows the clinician to suspect less common conditions such as syphilitic ostial stenosis, coronary embolization, pulmonary origin of a coronary artery, and necrotizing arteritis. Aneurysm of one or more coronary arteries, an infrequent condition as yet unrecognized clinically, is also likely to result in ischemic myocardial damage.[2-4] Since technical progress may yet permit surgical remedy of some of these conditions, physicians should be alert to the possibility of their occurrence.

We wish to report the case of a young man who died of ischemic heart disease secondary to unrecognized aneurysms of the coronary arteries.

Case Report

J. S., a 26-year-old, white, male college student, was admitted to the Veterans Administration Hospital, West Roxbury, on June 21, 1957. For the preceding 10 days he had experienced increasing exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.

His difficulties began about 2 years earlier when, after running, he experienced a syncopal attack. In the ensuing months there were 3 other nonconvulsive syncopal episodes, each related to exertion and some associated with oppressive substernal pain that radiated to the inner aspect of the left arm. Exertional angina also occurred without syncope, and there was a progressive decline in exercise tolerance. In October 1956 he was hospitalized at the Memorial Hospital in Worcester following a syncopal episode. Electrocardiography showed evidence of a posterior myocardial infarct. Radiologic studies with a Potter-Bucky diaphragm demonstrated an irregular ovoid mass (3 by 1.5 cm.), calcified like an egg shell, adjacent to the left upper border of a normal-sized cardiac shadow (fig. 1). Fluoroscopic examination revealed that the mass pulsated synchronously with the heart. Though not typical, it was considered to be a pericardial calcification. Despite the relative youth[5] of the patient, the other diagnoses were arteriosclerotic heart disease with angina pectoris and myocardial infarction.

At the age of 13 the patient had been hospitalized with a severe throat infection that responded to penicillin and salicylates. *Streptococcus viridans* was cultured from the throat. By x-ray, the heart was globular and enlarged, especially in the region of the right ventricle. Recovery was complete, however, and he was able to serve in the U. S. Navy from 1951 to 1955 without illness.

Physical examination upon admission demonstrated enlargement of the heart to the left, a protodiastolic gallop rhythm, and occasional extrasystoles. The blood pressure was 100/75 mm. Hg and the pulse rate was 88 per minute. Laboratory findings on blood, urine, and spinal fluid were unremarkable. The serologic test for syphilis (VDRL) was negative; serum cholesterol measured 153 mg. per cent of which 104 mg. per cent were esters; phospholipids were 192 mg. per cent. Serial electrocardiograms demonstrated a stable anteroapical myocardial infarct. Radiologic studies substantiated the impression of left ventricular enlargement and demonstrated pulmonary congestion initially, but not subsequently. Treatment consisted of digitalization, restriction of salt and fluids, and the administration of mercurial diuret-

From the Laboratory Service, Veterans Administration Hospital, West Roxbury, and Department of Pathology, Harvard Medical School and Department of Nutrition, Harvard School of Public Health, Boston, Mass.

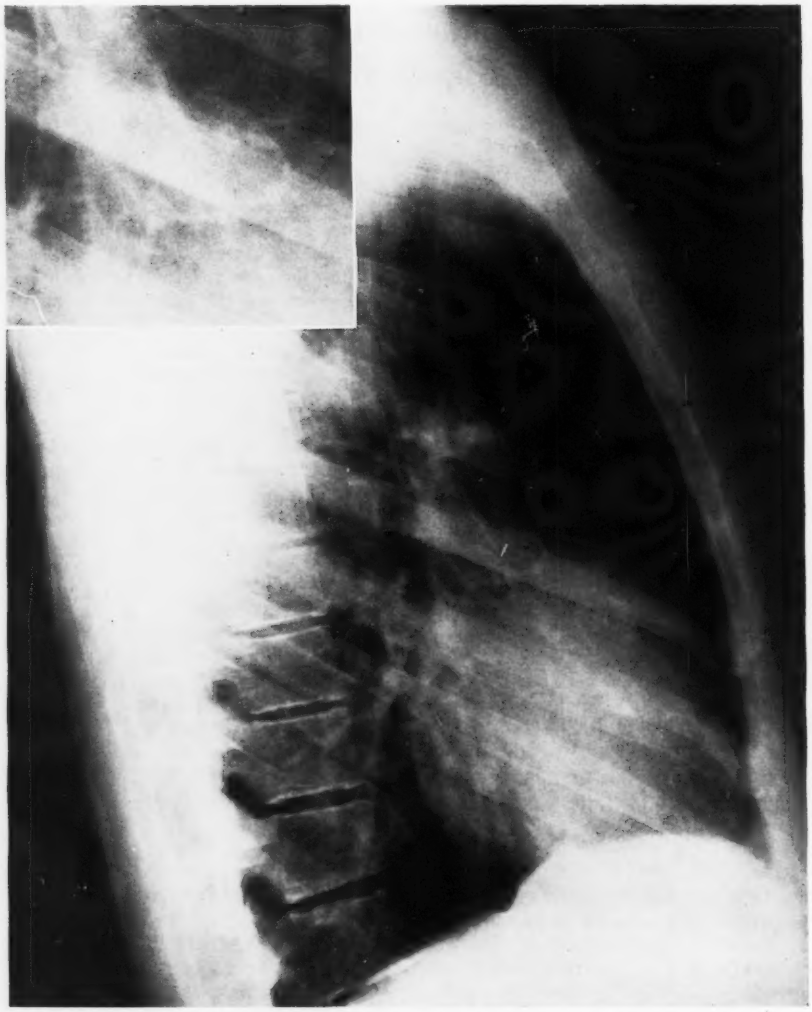


FIG. 1. Lateral x-ray (Potter-Bucky) of the chest. Note the shell-like opacity delineating a circular structure at the base of the heart in the angle between the anterior cardiac border and the conus. The detail of this area, slightly magnified, is shown in the *insert*. This structure corresponds with an aneurysm of the circumflex branch of the left coronary artery depicted in figures 2 and 3.

ies. On the assumption that the basic pathologic lesion was coronary atherosclerosis, despite the normal serum cholesterol values, he was placed upon a diet rich in unsaturated fatty acids. Nonetheless there was progressive deterioration, anginal attacks became more frequent, congestive failure reappeared and became increasingly difficult to control, and in November 1957, following a 4-day period of severe chest pain, he died.

At autopsy there was moderate left ventricular dilatation and myocardial hypertrophy, the heart weighed 490 Gm. A transmural scar (4 by 3.5 by 0.4 cm.) replaced a portion of the posterior left ventricular wall. The remainder of the posterior wall presented foci of muscle loss and subendocardial fibrosis which were pale gray at the base and red-gray and vascular toward the apex. The interventricular septum was thinned where its an-

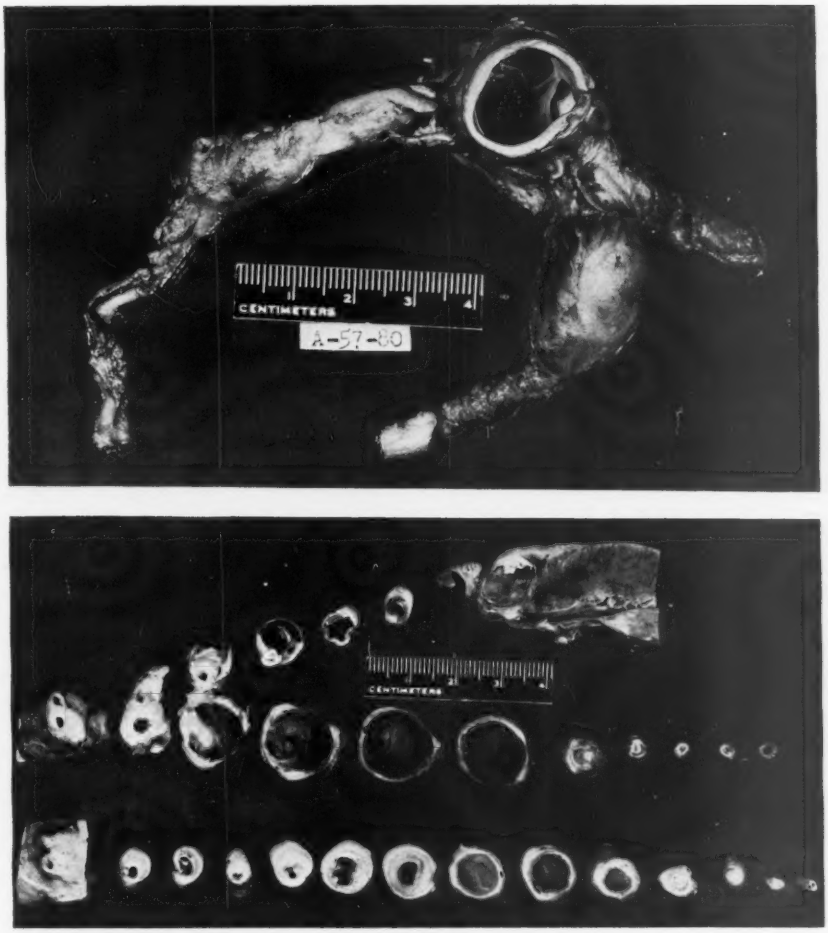


FIG. 2. *Top.* Dissected coronary arterial tree and aortic root viewed from above, showing diffuse aneurysmal dilatation of the right coronary and of the 2 branches of the left coronary artery. *Bottom.* Serial transections of the coronary arterial tree. The lowermost vessel is the right coronary artery; above it lie respectively the anterior descending and circumflex rami of the left coronary artery. The aneurysms are filled with thrombi of varied age and organization.

erior two thirds was largely replaced by vascularized scar tissue. Except for diffuse endocardial hickening the anterior wall of the left ventricle vas unremarkable. The valves were competent with tructurally intact, undeformed, pliable leaflets.

There were large fusiform aneurysms of the 3 major coronary rami (figs. 2 and 3). The circumflex and the anterior descending arteries arose from normal-sized adjoining ostia in the left aortic sinus and expanded immediately. The aneurysm of the anterior descending branch extended distally for 3.2 cm. and measured 1.5 cm. in its greatest diameter. Its wall contained egg-shell-like deposits of calcium. Serial transection after decalcification revealed a large lumen, 1.3 cm. across, completely filled with concentrically laminated, mottled gray-white and dark red, friable thrombus. Distally the aneurysm tapered gently into an 0.4-cm. artery with thin pliable walls devoid of intimal disease. The aneurysm of the circumflex artery measured 4 by 1.2 cm.; there was a small eccentric residual lumen, but in all other respects it was identical with the anterior descending ramus. The right coronary artery arose from a normal-sized

FIG. 3. Low-power photomicrograph of the left circumflex coronary aneurysm in situ in the left-atrioventricular sulcus. A transection of the mitral valve at the left distinguishes the endocardial aspect. Except for a relatively small lumen containing fragments of fresh thrombus, the aneurysm is filled with degenerating blood clot. The space at the upper left of the aneurysm is an artefact. At the lower right, partially encircling the persistent channel, the thrombus is organized.

aortic ostium. There was a small accessory right coronary ostium which fed a short vessel to the right ventricle. After a course of 0.8 cm. the main ramus expanded into a fusiform aneurysm 5.1 cm. long and 1.2 cm. in greatest diameter. Distally it tapered into a channel 0.4 cm. wide which exhibited focal thickening by firm gray-white tissue and severe luminal narrowing 3.2 cm. beyond the aneurysm. This aneurysm, like that of the descending ramus of the left coronary artery, was totally occluded by concentrically laminated, gray-tan to red thrombus.

The aorta was smooth with only a moderate quantity of linear flat yellow intimal deposits in its abdominal portion.

The lungs and viscera were moderately congested.

Microscopically, the left ventricular myocardium presented extensive areas of subendocardial and transmural scarring; additionally, there were small foci of recent ischemic necrosis involving the right ventricular myocardium. The walls of the coronary aneurysms were essentially fibrous with focal calcific deposits and only tiny vestiges of elastica or medial musculature. Except for a small lumen in the left circumflex the 3 aneurysms were completely filled with thrombus of varying age and organization. Related to the organization of the thrombi were small accumulations of lymphoid cells about thin-walled vascular channels in the aneurysmal wall. Uninvolved segments of the coronary arterial tree presented small focal gaps and defects in the medial musculature without associated inflammation.

DISCUSSION

In the present case the structure of the aneurysms and the absence of septicemia or of endocarditis clearly rule out bacterial infection as an etiologic factor. Similarly, the clinical history and course as well as the anatomic findings negate the possibility of syphilis, rheumatic fever, or necrotizing arteritis. The distinction, accordingly, lies between congenital and arteriosclerotic aneurysm. In this instance, with organizing thrombi filling the dilated channels, this differential cannot be made on structure alone. The secondary intimal changes, which result from the organization of mural thrombi, duplicate the usual features of atherosclerosis.[6] The replacement of specific vascular structure by fibrous tissue with calcific deposits too has no differential diagnostic value. Atherosclerosis, however, is a generalized pathologic process though its clinical manifestations may be local, and it is extremely unlikely that it may be so advanced that it causes aneurysms in the coronary arteries while there is only insignificant or early disease in the aorta and elsewhere. Indeed it has been demonstrated that atherosclerosis is generally more severe and advanced in the aorta than in other areas.[7] Accordingly, we think that the aneurysms were congenital rather than arteriosclerotic. Obviously, this distinction could not have been made clinically, but an awareness of coronary aneurysm as an entity might have allowed us to interpret the radiologic findings differently and to place more significance upon the normal serum cholesterol values. There are undoubtedly many exceptions to the gen-

ralization that there is a positive correlation between elevated serum cholesterol levels and coronary atherosclerosis.[8] In the younger age groups, however, exceptions of this nature are fewer[9] and one must urge that other possibilities be considered before concluding that a given case is such an instance.

The basis for the formation of any aneurysm is a structural weakening of the vessel wall; the actual causative mechanism, of course, is variable. Only too often, as in this case, the aneurysmal wall is essentially scar tissue, and except for lesions associated with violent or even necrotizing inflammation, little or no evidence remains to indicate the nature of the original lesion. Clues are sometimes to be found in relatively uninvolved segments of the diseased vessels. We consider that the small focal medial defects of "uninvolved" segments are representative of the lesions which, in greatly augmented form, weakened the affected portions of the coronary arteries sufficiently to lead to aneurysmal dilatation. It will be recalled that Forbus[10] demonstrated somewhat similar lesions as the basis for congenital berry aneurysms at the bifurcations of cerebral arteries.

The designation of an aneurysm as congenital implies only that the basic cause is developmental. The actual exploitation of the structural weakness by aneurysmal dilatation may occur during the neonatal period[3] but may not appear for decades. Dilatation of the affected channel creates an additional burden that contributes to further growth of the aneurysm, since, hydrodynamically, the tension to which the wall of a channel is subject increases with its diameter.[11] In the process there is progressive attenuation and atrophy of residual elements of the vessel wall. Fibrous repair and reinforcement tend to limit expansion, but usually without success. Even the occurrence of calcification within the wall of the aneurysmal sac, since it is patchy, does not prevent further growth. Thrombosis, a complication to which aneurysms are vulnerable because of slowing and turbulence of the blood stream, may through organization contribute to fibrous reinforcement of the sac wall. In the case of an aneurysm of the coronary artery, however, this sequence may be lethal, as in our case. Even nonocclusive mural thrombosis within a coronary aneurysm is not without hazard. First, the propensity of a clot to propagate may lead to complete occlusion. This situation is exemplified again by our case, in which the occluded aneurysms showed evidence of episodic clotting with recent thrombi superimposed upon older organized and organizing thrombi. Second, dislodgment of a mural thrombus, favored by the expansile pulsation of the aneurysmal sac, may lead to distal embolization. One wonders if this could not have been true in some of the cases reported with thrombosis distal to a coronary arterial aneurysm.[3]

TABLE 1.—*Aneurysms of Coronary Arteries (69 Cases)*

Specified location		66
Left coronary artery	35	
Right coronary artery	20	
Left and right coronary artery	11	
Multiple aneurysms		10
Single aneurysms		56

According to Packard and Wechsler,[4] the first report of an aneurysm of the coronary artery was made by Bougon[12] in 1812. By 1929, 2 probable cases of periarteritis nodosa being excluded, 28 cases had been described; by 1948[2] the number had risen to 45, and by 1957[3] there were 68. Etiologically, as shown in the accompanying table, more than half the reported cases are of congenital or arteriosclerotic origin. Current experience, moreover, suggests an even greater predominance, since the septic states that cause mycotic-embolic aneurysms are now much more readily managed and there is a reduced incidence of syphilis and rheumatic fever. Similarly, other differences between older and more recent experience may be related to the diminished frequency of infectious forms of aneurysm. Scott[2] had noted that coronary occlusion predominated as a cause of death, whereas aneurysmal rupture was more frequent in the earlier series of Packard and Wechsler.[4] As is evident in table 1, the left coronary artery has been involved much more frequently than

TABLE 2.—*Etiologic Classification and Age and Sex Distribution of Aneurysms of the Coronary Arteries*

Decade	1	2	3	4	5	6	7	8	9		
Congenital	2M	1M	2M	3M	1M	2M	3M	2M	1M	Rupture	4
17M 4F	2F					2F*				Thrombosis or infarction	4
Arteriosclerotic					2M	5M	4M	3M		Rupture	1
14M 3F							1F	1F	1F	Thrombosis or infarction	8
Mycotic	1M	1M	2M	2M	1M					Rupture	4
7M 5F		3F	1F		1F					Thrombosis or infarction	2
Syphilitic				1M					1M	Rupture	1
2M 1F					1F					Thrombosis or infarction	2
Rheumatic	1M										
1M										Thrombosis or infarction	1
Unclassified	2M			2M						Rupture	1
4M 2F			1F	1F						Thrombosis or infarction	1

Total (All types) 45M 15F (9 other cases had insufficient information to be tabulated.)
*One case considered arteriosclerotic as well as congenital.

the right, but Crocker et al.[3] did not find this to be true in the most recent series of 20 cases.

There were aneurysms of both coronary arteries in 11 cases; in 6 of that group the lesions were congenital. As shown in table 2, aneurysms of the coronary arteries are several times more frequent among males than females. The sex disparity is even greater if consideration is limited to the most frequent forms, congenital and arteriosclerotic. Age-wise, arteriosclerotic aneurysms are essentially lesions of the older age groups, whereas those of congenital origin occur at any age. One of the lesions tabulated herein as congenital was considered by the author[13] to be arteriosclerotic as well. For those congenital lesions that do not appear until late in life at least, it seems reasonable to suspect that factors associated with aging are an important complement to the basic developmental lesion.

SUMMARY

We have reported a case, the sixty-ninth of coronary artery aneurysm, the twenty-first of congenital aneurysm of the coronary artery, the sixth in which both coronary arteries were involved, and the first in which a coronary aneurysm was visualized, though not recognized, during life.

The patient had symptoms of myocardial anoxia for 2 years prior to his death from myocardial infarction. One year before his demise an x-ray film of the chest, taken with a Potter-Bucky diaphragm, had demonstrated a calcified ovoid mass, which subsequent autopsy proved to be an aneurysm involving the circumflex branch of the left coronary artery.

We have discussed the differential pathologic features of congenital and arteriosclerotic aneurysms and have tabulated some of the statistical information of the reported cases, including for completeness, other etiologic causes of the lesion.

SUMMARIO IN INTERLINGUA

Le caso que nos reporta es le sexanta-nove de aneurysma de arteria coronari, le vinti-prime de aneurysma congenite de arteria coronari, le sexte in que ambe arterias coronari

s afficite, e le prime in que un aneurysma oronari esseva visualisate—ben que non reognoscite—durante le vita del patiente.

Le patiente habeva symptomas de anoxia nyocardial durante 2 annos ante su morte ab nfarcimento myocardial. Un anno ante su norte, un roentgenogramma thoracic, obtenite on un diaphragma Potter-Bucky, demonstrava un calcificate massa ovoide. Le necropsia revelava subsequentemente que ille "massa" esseva un aneurysma que afficeva le branca circumflexe del arteria sinistro-coronari.

Nos ha discutite le aspectos pathologic de interesse pro le differentiation de aneurysmas congenite ab aneurysmas arteriosclerotic e ha summarisate in forma tabular le informationes statistic del casos reportate in le litteratura. Pro render le presentation complete, altere causas etiologic del lesion es includite.

REFERENCES

1. Gould, S. E.: Vascular lesions of the heart. *In* Pathology of the Heart, S. E. Gould, ed. Springfield, Ill., Charles C Thomas, 1953.
2. Scott, D. H.: Aneurysm of the coronary arteries. Am. Heart J. **36**: 403, 1948.
3. Crocker, D. W., Sobin, S., and Thomas, W. C.: Aneurysms of the coronary arteries: Report of three cases and review of the literature. Am. J. Path. **33**: 819, 1957.
4. Packard, M., and Wechsler, H. F.: Aneurysm of the coronary arteries. Arch. Int. Med. **43**: 1, 1929.
5. Yater, W. M., Traum, A. H., Brown, W. G., Fitzgerald, R. P., and Geisler, M. A.: Coronary artery disease in men 18 to 39 years of age: Report of 866 cases, 450 with necropsy examination. Am. Heart J. **36**: 334, 481, 683, 1948.
6. Duguid, J. B.: Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. J. Path. & Bact. **58**: 207, 1946.
7. Gore, I., and Hirst, A. E., Jr.: Comparative severity of atherosclerosis in the aorta, coronary arteries, and cerebral arteries. Am. J. Path. **33**: 595, 1957.
8. Gertler, M. M., Garn, S. M., and Bland, E. F.: Age, serum cholesterol, and coronary artery disease. Circulation **2**: 696, 1950.
9. Gofman, J. W., Glazier, F., Tamplin, A., Strisower, B., and DeLalla, O.: Lipoproteins, coronary heart disease and atherosclerosis. Physiol. Rev. **34**: 589, 1954.
10. Forbus, W. D.: On the origin of miliary aneurysms of the superficial cerebral arteries. Bull. Johns Hopkins Hosp. **47**: 239, 1930.
11. DeTakats, G., and Pirani, C. L.: Aneurysms: General considerations. Angiology **5**: 173, 1954.
12. Bougon: Bibl. Med. **37**: 183, 1812 (cited by Packard and Wechsler[4]).
13. Dordi, F.: Descrizione di un raro caso di aneurisma dell'arteria coronarica sinistra. Pathologica **42**: 239, 1950-51.

Rose, G. A., and Spencer, H.: Polyarteritis Nodosa. Quart. J. Med. **26**: 43 (Jan.), 1957.

One hundred eleven proved cases of polyarteritis nodosa were classified according to the presence or absence of lung involvement. In the cases with lung involvement, a respiratory infection preceded and dominated the illness. Blood and tissue eosinophilia was present and, microscopically, a granulomatous polyarteritis or necrotizing lesions not necessarily related to arteries were demonstrated. The theories of the pathogenesis are reviewed. Evidence points to an association with preceding respiratory infections, especially those due to streptococcus and with rheumatic fever. Of the many drugs incriminated, sensitivity to thiouracil drugs seemed to be the only valid relationship. Necropsy findings were reviewed in 86 patients in whom blood pressure records were adequate. Among 48 patients whose blood pressure remained normal, recent renal polyarteritis and glomerulitis were common; but healed lesions were rare. In 14 of 17 patients who developed hypertension during the disease and 21 patients whose blood pressure was high when first measured, healed renal polyarteritis was found.

Kurland

SPECIAL ARTICLE

Biochemical Alterations in Blood in Obliterative Atherosclerosis

By KORNEL GIBIŃSKI, M.D.

Biochemical alterations in blood due to pathologic changes in the legs are difficult to detect when the blood samples are taken from the cubital vein. In the reported investigations biochemical properties of this blood are compared with those of the venous blood flowing out from a leg affected by obliterative atherosclerosis.

ATHEROMATOUS processes developing in the walls of the arteries as well as any consequent tissue ischemia necessarily produce biochemical alterations in the blood. The changes in the venous blood draining from the area affected by such atherosclerotic lesions become more difficult to detect, as this blood mixes with that from regions without vascular changes. Therefore venous blood from the leg affected by obliterative atherosclerosis was compared with venous blood of the upper extremity showing no detectable vascular changes. Oxygen saturation (Van Slyke method), serum protein level (refractometer) and its electrophoretic spectrum (paper electrophoresis), lipoproteins, serum cholesterol (Zlatkis), and total lipids (Swahn), serum glutamic-oxalacetic and glutamic-pyruvic transaminases activity (Reitman and Frenkel), serum aldolase activity (Lehninger, Bruns), proteolytic activity of plasma and total blood (Balachowski and Balachowski), and amino acid levels (Folin) and composition in the blood serum (paper circular chromatography) were examined.

From the Third Clinic of Internal Diseases, Silesian School of Medicine, Bytom, Poland.

This paper was presented at the Fifth Congress of the International Society of Internal Medicine in Philadelphia, Pennsylvania, U.S.A., April 23 to 26, 1958. Its substance was presented at the Nineteenth Congress of the Polish Society of Internal Medicine in Poznan, Poland, September 26 to 28, 1957.

RESULTS

No significant differences were found in these components of the blood taken from upper and lower extremities of healthy control subjects. In 25 patients suffering from obliterative atherosclerosis of lower extremities, the total protein level showed no changes, but hypoalbuminemia and hyperglobulinemia (especially gamma) were commonly found. Only the alpha$_1$ globulin level was constant, and always within normal ranges (table 1). The lipoprotein index was found to be increased in one quarter of the cases and was high more often in patients with generalized atherosclerosis. It should be noted that, on the contrary, in Buerger's disease the lipoprotein index is always normal. No differences were obtained between the protein and lipoprotein patterns in the blood samples taken from the leg and the arm.

We did not observe any characteristic alterations in the cholesterol level. The total lipid level was increased in one third of the cases. This finding was, however, independent of the degree of morbid change and of the vein from which the blood was taken. An increase in the plasma transaminase activity was found in these cases. This was more marked and more constant in the venous blood of the affected leg than of the healthy arm, which suggests that a necrotic area was a source of the increased transaminase (fig. 1).

TABLE 1.—*Blood Plasma Protein and Its Electrophoretic Spectrum*

Patient	Age	Total protein	Albumin (%)	Globulin				Lipoprotein index		Local changes
				α_1	α_2	β	γ	Arm	Leg	
P.F.	60	8.17	45.4	1.6	7.4	9.0	36.6	1.5	1.6	Very serious
R.F.	76	7.89	46.3	4.1	11.8	19.2	18.6	2.5	2.5	Very serious
M.H.	63	7.6	58.0	3.0	8.0	10.0	21.0	4.5	4.5	Serious
J.J.	54	8.17	52.3	2.8	8.0	15.3	21.6	6.8	5.2	Serious
P.O.	52	7.6	49.0	1.7	12.1	14.9	22.3	1.4	1.1	Serious
E.P.	65	8.17	30.5	2.1	18.4	23.5	25.5	2.3	2.3	Serious
S.K.	63	8.75	53.3	1.4	10.4	13.1	21.8	0.8	0.8	Serious
W.O.	70	8.17	65.0	3.5	5.0	9.0	17.5	1.0	1.0	Serious
P.G.	64	8.17	47.3	2.8	9.2	15.1	25.6	1.8	1.8	Serious
W.Z.	63	8.17	58.2	1.0	10.8	9.9	20.1	2.0	2.2	Serious
H.W.	59	8.17	58.5	3.0	5.5	11.3	21.7	1.0	1.0	Serious
S.S.	57	8.17	55.0	3.8	9.6	14.7	16.9	0.8	0.8	Serious
A.L.	51	8.69	44.0	3.5	13.5	18.7	20.3	2.8	2.0	Mild
P.H.	51	6.42	50.0	4.1	13.6	17.7	14.6	2.3	2.3	Mild
K.B.	60	8.17	45.0	4.6	11.2	13.6	25.6	2.8	3.0	Mild
T.K.	67	8.17	40.0	2.6	9.4	15.0	33.0	1.7	1.7	Mild
W.T.	61	8.17	48.7	2.7	8.6	17.7	22.3	0.9	0.9	Mild
W.G.	55	8.11	57.0	1.5	11.5	15.0	15.0	1.8	1.1	Mild
J.Sz.	53	7.6	45.2	2.8	11.8	13.2	27.0	0.9	0.9	Mild
Average		8.0	49.9	2.7	10.3	14.5	22.5	2.0	2.0	Mild

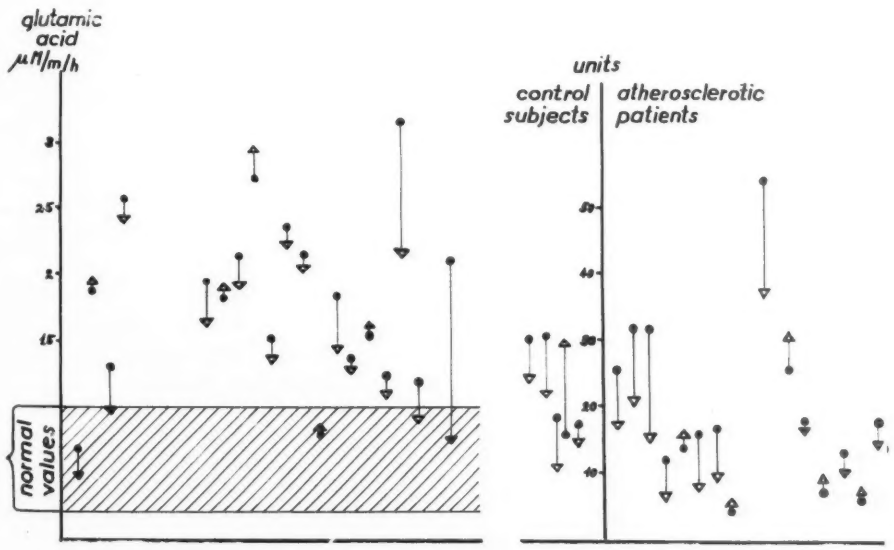


FIG. 1 *Left.* Serum glutamic pyruvic transaminase activity in the blood plasma of the ailing lower extremity (*closed circle*) and in the plasma of the healthy upper extremity (*triangle*). Nearly all values exceed normal, those referring to the legs being higher.

FIG. 2 *Right.* Serum aldolase activity in healthy subjects was similar to that in atherosclerotic patients, except 1 case.

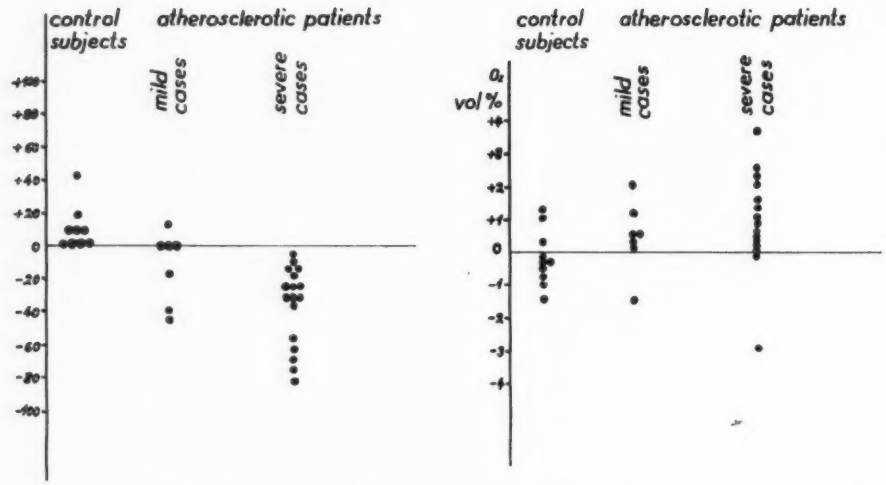


FIG. 3 *Left.* Proteolytic activity of the whole blood of the lower ailing extremity as compared with that of the upper healthy extremity.

FIG. 4 *Right.* Oxygen saturation of the venous blood from the lower ailing extremity as compared with that of the upper healthy extremity.

It affected the serum glutamic pyruvic transaminase activity more than it did the serum glutamic oxalacetic transaminase.

The presence of sizable necrotic lesions in the foot was not essential in producing these changes; these lesions may be quite insignificant in size or not visible at all. There exists no close relation between transaminase levels and the symptoms of intermittent claudication. The latter is not dependent on actual necrosis but reflects ischemia which does not necessarily provoke release of transaminase into the blood stream. A fall in plasma transaminase activity toward normal during successful treatment was often seen.

In the same conditions no marked rise of serum aldolase was observed (fig. 2). The most impressive alteration was the decrease of proteolytic activity of the blood from the damaged lower extremity as compared with that of the upper extremity. No close relation was evident between the intensity of lesions and symptoms and the decreased proteolytic activity of the blood. In general, however, the decrease was not so marked in the group with more severe lesions as among the patients with slight local changes. It occurred in all cases and tended to return to normal with improvement of the clinical state (fig. 3). This proteolytic activity is bound with the cellular components of the blood and seems to be identical with coagulolysis.

The determination of total serum amino acid levels and their composition did not show any significant changes.

The impaired utilization of oxygen is detectable in the area affected by obliterative atherosclerosis (fig. 4). No relationship was found between the quoted biochemical findings and the oxygen utilization.

In the evaluation of the clinical state not only the vascularization of the extremity and possible oxygen supply to the tissues, but also the oxygen demand and metabolism of the tissues should be taken into account.

SUMMARY

Twenty-five patients with peripheral obliterated atherosclerosis were examined. The typical plasma protein changes, serum cholesterol, and total lipid levels were independent of the vein from which the blood samples were taken. Serum glutamic-pyruvic transaminase activity was higher in the blood taken

from the affected area than in the control blood from the antecubital vein. Serum aldolase activity did not show any characteristic alterations. The blood from the affected leg showed decreased proteolytic activity, especially in the severer cases. It is related to the cellular components of the blood. The oxygen utilization by the tissues was decreased in the area normally supplied by the damaged vessels.

SUMMARIO IN INTERLINGUA

Vinti-cinque patientes con peripheric atherosclerosis oblitterative esseva examinate. Le typic alterationes del proteina in le plasma, le cholesterol del sero, e le nivellos total de lipido non variava con le venas ab le quales le specimens de sanguine esseva prendite. Le activitate de transaminase glutamic-pyruvic esseva plus intense in le sanguine prendite ab le area affecte que in le sanguine de controlo ab le vena antecubital. Le activitate de aldolase in le sero monstrava nulle alterationes characteristic. Le sanguine ab le gamba affecte monstrava un reducite activitate proteolytic, specialmente in le casos plus sever. Iste phenomeno es relationate con le componentes cellular del sanguine. Le utilisation de oxygeno per le histos esseva reducite in le area que es normalmente alimentate per le vasos damnificate.

Bulle, P. H.: Chlorpromazine and Reserpine Prevention of Myocardial Damage by Histamine and Serotonin. Science **126**: 24 (July 5), 1957.

Destruction of blood cells during clotting, such as in myocardial infarction, may release serotonin and histamine within the cardiac muscle. This problem was studied in the isolated perfused rabbit heart. Reserpine and chlorpromazine were tested with respect to their effectiveness in altering the action of serum, histamine, and serotonin on the functioning of the heart and coronary flow. Serotonin injection into the wall in minute amounts rapidly induced an "infarct," as determined by dye visualization. Histamine also produced infarction but more slowly. Reserpine had no effect on infarct formation induced by serum, serotonin, or histamine. Chlorpromazine, however, in the low dosage used did prevent these "infarcts." Although these experiments may suggest that chlorpromazine could be used "as an adjuvant in prophylactic treatment of myocardial infarction," the author himself points out that there is a question whether this study exactly parallels the conditions in clinical infarction. Quantitative determinations of histamine and serotonin in infarcted areas of the human heart would need to be made. Further work is clearly indicated.

WAIFE

The Pulmonary Diffusing Capacity in Congenital and Rheumatic Heart Disease

By J. Howland Auchincloss, Jr., M.D., Robert Gilbert, M.D., and Robert H. Eich, M.D.

The pulmonary diffusing capacity was determined both in patients with intracardiac septal defects and in patients with valvular heart disease in an effort to find out whether pulmonary congestion and hyperemia as they occur in cardiac disease have different effects on the process of gas diffusion and whether these effects vary at different stages of the disease process.

THE pulmonary diffusing capacity (DL) is a measurement relating the flow rate of gas across the alveolo-capillary membrane to the pressure gradient. Estimation of DL is possible by a variety of technics,[1] and in recent years it has resulted in a materially improved understanding of diffuse pulmonary parenchymal disease[2] and of the effect of chronic airway obstruction on the pulmonary parenchyma.[3, 4] The effect of heart disease on DL has not received comparable attention; however, Carroll, Cohn, and Riley[5] have demonstrated that DL at rest may or may not be reduced in disease of the mitral valve.

Classically, the magnitude of DL has been considered to depend upon the permeability of the diffusing surface and the amount of area available for diffusion. In addition, Roughton and Forster[6] have recently shown that DL is also affected by the volume of blood in ventilated pulmonary capillaries. It would seem reasonable that both the surface area and capillary blood volume might be increased under conditions of passive congestion, as in mitral valve disease, and under conditions of increased pulmonary blood flow (pulmonary hyperemia) such as occurs in septal defects with left-to-right shunts. Also, it might be expected that either of these conditions could eventually affect the permeability of the membrane. Thus, alterations of the diffusing capacity in cardiac disease could be a result of the effects of the disease on any or all of the determinants of diffusing capacity and might give valuable information concerning both the circulatory and parenchymal state of the lungs.

From the Department of Medicine, State University of New York Upstate Medical Center and Veterans Administration Hospital, Syracuse, N. Y.

This study was aided by a grant from the U.S. Public Health Service.

Presented before the Thirtieth Scientific Session of the American Heart Association, Chicago, October 1957.

Materials and Methods

The clinical and hemodynamic data for the 29 patients included in the study are summarized in table 1. In 16 of these patients the diagnosis of interatrial or interventricular septal defect had been established by right heart catheterization. Atrial defects (IASD) with or without anomalous pulmonary veins existed in 13 patients; in 7 of these the mean resting pulmonary artery pressure was 22 mm. Hg or less. The remaining 6 patients with IASD exhibited evidence of pulmonary hypertension; in 4 cases this was established by direct measurement (mean pulmonary artery pressure 33 to 72 mm. Hg), but in 2 patients (nos. 15 and 16) the catheter failed to enter the pulmonary artery. Pulmonary hypertension was considered likely in 1 of these 2 patients (no. 15) because she had undergone multiple episodes of severe right heart failure. Pulmonary hypertension was considered to be present in patient no. 16 because the catheter entered the right ventricle, where a systolic pressure of 84 mm. Hg was recorded. In the absence of clinical evidence of pulmonic stenosis, this figure undoubtedly is close to the pulmonary artery systolic pressure, and therefore permits an estimation of pulmonary artery mean pressure (50 mm. Hg) for correlative purposes.

Three patients had interventricular septal defects (IVSD). Pulmonary artery pressure was normal in 1 and elevated in 2.

In the entire group (IASD and IVSD) shunt reversal at rest was clinically manifest in only 1

case (no. 11, IVSD), in whom arterial oxygen saturation was 79 per cent. However, values less than 93 per cent (the lower limit of normal in this laboratory) were found in 4 additional patients. In patient no. 16 arterial oxygen saturation fell from a resting value of 91 to 69 per cent following the standard exercise test, suggesting that reversal of shunt with exercise had occurred.

The 13 patients with rheumatic heart disease have been grouped in tables 1 and 2 according to the manometric or clinical estimation of pulmonary artery pressures. Five of these patients were considered by clinical examination to have normal pulmonary artery pressures; in the 2 instances in which doubt existed (nos. 18 and 20) catheter measurements were obtained. The remaining 8 cases were, with 1 exception, in an advanced or unquestionably progressive stage of the disease; case no. 24 presented very mild symptoms but definite resting pulmonary hypertension.

A control series of 19 normal subjects was selected on the basis of good general health and absence of known cardiac or pulmonary disease. Four of the group were hospitalized patients and 15 were doctors, technicians, or hospital personnel.

The standard technics used in physiologic diagnosis and evaluation of the cardiac patients have been described in a previous report from this laboratory.[7] In the present study oxygen saturation determinations in some instances were made with a Wood-type oximeter as an adjunctive device at cardiac catheterization. Shunt localization in case no. 10 was accomplished by injection of radioactive iodinated serum albumin through the catheter at different sites in the right heart. Cardiac output in some of the subjects with rheumatic heart disease was determined by the dye-dilution technic, which in this laboratory correlated satisfactorily with the Fick method.

The resting diffusing capacity for carbon monoxide (DL_{CO}) by the single-breath technic was carried out as described by Ogilvie et al.[8] Subjects and patients came to the laboratory in the postprandial state. Estimation of the total lung capacity and its subdivisions was performed by spirometry and the nitrogen washout technic[9] with the subject seated. The disappearance rate of carbon monoxide from the alveolar air was then measured during a breath-holding period of 10 to 13 seconds. The subject performed as complete an expiration as possible and then was switched into an atmospheric circuit previously washed out with the test gas. Inhalation was as rapid as possible and as complete as could be achieved without a maximum effort. The command for a complete expiration was given 10 seconds after inspiration was completed, but the duration of breath holding was timed by the graphic tracing from the beginning of inspiration to the collection of the alveolar

TABLE 1.—*Clinical and Hemodynamic Data*

Case No.	Diagnosis	Am. Heart Assoc. functional capacity	Pulmon. artery pressure (mean) (mm. Hg)	Pulmon. blood flow index (L./min./M.²)	Systemic blood flow index (L./min./M.²)	Arterial O_2 saturation (%)
Congenital Heart Disease						
Pulmonary hypertension absent or mild						
1	IVSD	I	14	7.4	3.4	94
2	Anomalous pulmonary venous drainage† IASD	I	22	9.2	3.5	98
3	IASD	I	21	8.0	5.3	93
4	IASD	I	18	6.0	3.5	96
5	IASD	II	20	19.0	7.3	91
6	IASD	I	14	9.2	2.2	95
7	IASD	I	15	27.0	4.7	95
8	IASD	II	15	14.0	5.2	99
Pulmonary hypertension moderate or severe						
9	IVSD	I	46	14.0	5.0	95
10	IASD, right-to-left shunt	II	72	2.7	3.2	91
11	IVSD, right-to-left shunt	II	96	1.3	2.5	79
12	IASD, ost. prim. and secund.	III	34	6.7	2.1	97
13	IASD, ost. prim. and secund.	III	49	3.6	2.0	92
14	IASD, tricuspid insufficiency	II	33	22.0	3.3	97
15	IASD	III	—	6.7	2.4	94
16	IASD, ost. prim.	III	(50)*	4.3	2.8	91
Rheumatic Heart Disease						
Normal pulmonary artery pressure at rest, or mild symptoms						
17	MS	I				
18	MS	I	14	2.5	2.5	97
19	MS	I				
20	MS	I	16	4.0	4.0	91
21	MS	I				
Pulmonary arterial or left atrial hypertension at rest, or moderate to severe symptoms						
22	MS, MI	III	38			90
23	MS, AI	III	18†	2.8	2.8	95
24	MS	II	24	3.0	3.0	95
25	MI	III	—	—	—	—
26	MS, AS	III	23	—	—	93
27	MS, progressive dyspnea, hemoptysis	III	—	—	—	—
28	MS	III	25	3.0	3.0	93
29	MI	III	26†	1.9	1.9	91

*Pulmonary artery mean pressure estimated from right ventricular systolic pressure.

†Left atrial pressure.

IVSD, interventricular septal defect; IASD, interatrial septal defect; MS, mitral stenosis; MI, mitral insufficiency; AI, aortic insufficiency; AS, aortic stenosis.

TABLE 2.—*Lung Volumes and Diffusing Capacity*

Case No.	Age	Sex	Ht. (cm.)	BSA ($M.^2$)	Vital capacity (L.) obs.	Vital capacity (L.) % pred.	Residual volume/ total lung capacity (%)	Mixing index (% N_2)	Max. breathing capacity (L./min.) obs.	Max. breathing capacity (L./min.) % pred.	DL_{CO} obs. (ml./ min./ mm. Hg)	DL_{CO} pred. (ml./ min./ mm. Hg)	DL_{CO} % pred.
Congenital Heart Disease													
Pulmonary hypertension, absent or mild													
1	19	M	171	1.84	4800	99	21	0.67	165	117	40	28	143
2	20	M	173	1.71	4820	77	26	0.95	137	105	51	28	182
3	31	M	167	1.64	3250	72	25	0.94	144	125	33	26	127
4	35	M	184	2.11	4120	81	30	0.70	158	112	37	32	116
5	45	M	176	1.73	3390	77	37	0.90	134	123	47	29	162
6	49	M	173	1.91	4180	101	30	0.97	128	110	40	28	143
7	17	F	163	1.58	2830	85	28	1.23	75	75	32	25	128
8	32	F	162	1.58	2690	84	33	1.03	79	91	32	24	133
Pulmonary hypertension, moderate or severe													
9	16	M	173	1.90	4830	96	17	0.54	199	134	35	28	125
10	20	M	175	1.83	4730	90	31	0.46	193	139	36	29	124
11	30	M	175	1.98	4400	90	24	0.44	161	115	30	29	103
12	39	M	171	1.72	3650	83	37	0.67	138	121	30	28	107
13	19	F	152	1.35	1350	49	54	1.03	41	48	24	20	120
14	29	F	166	1.52	2210	64	42	0.73	73	83	32	26	123
15	38	F	158	1.80	1930	66	46	0.90	41	43	30	23	130
16	47	F	155	1.32	2060	79	40	2.16	54	83	11	22	50
Average	30	—	168	1.72	3453	81	33	0.90	120	102	34	27	126
Range	16-49		152-184	1.32-2.11	1350-4830	49-101	17-54	0.44-2.16	41-199	43-139	11-51	20-32	50-182
Rheumatic Heart Disease													
Normal pulmonary artery pressure at rest or mild symptoms													
17	23	M	155	1.58	3710	88	25	0.69	54	46	28	22	127
18	29	F	162	1.49	3420	105	27	0.64	82	96	26	24	108
19	31	F	155	1.52	3260	111	27	1.47	117	136	21	22	95
20	35	F	163	1.63	3290	104	23	1.24	106	118	23	24	96
21	38	F	155	1.48	3410	122	30	0.57	90	114	21	22	95
Pulmonary artery or left atrial hypertension at rest or moderate or severe symptoms													
22	31	M	174	1.73	3510	73	32	0.83	130	107	19	29	66
23	33	M	183	1.87	3980	77	30	1.59	221	170	27	32	84
24	46	M	182	1.96	5560	120	26	2.28	154	125	26	32	81
25	47	M	161	1.76	3970	109	29	1.10	149	137	26	24	108
26	25	F	162	1.59	1730	49	40	0.54	74	78	14	26	54
27	30	F	159	1.47	2690	86	41	0.86	87	104	25	23	109
28	38	F	167	1.58	2460	75	41	1.08	106	126	18	26	69
29	50	F	165	1.61	1920	65	41	0.97	59	78	14	25	56
Average	35	—	165	1.64	3301	91	32	1.07	110	110	22	25	88
Range	23-50		155-183	1.47-1.96	1730-5560	49-122	23-41	0.54-2.28	54-221	46-170	14-28	22-32	54-127

sample and was therefore always in excess of 10 seconds. The valve that switched the patient into the circuit for collection of the alveolar sample was turned when the operator sensed that expiration had begun, and the short time delay necessary for turning the valve allowed about 700 to 2,000 ml. of dead space and alveolar air to escape. The alveolar sample, collected in a 6 liter anesthesia bag, was transferred to the gas analyzers under positive pressure. Thermal conductivity (helium) and infra-red (carbon monoxide) meters were connected in series, and all analyses were performed after the removal of water vapor. The helium analyses were performed both before and after the removal of carbon dioxide by absorption, and thus the percentage of carbon dioxide could be estimated with an accuracy of 1 per cent. Appropriate corrections were then applied to both the helium and carbon monoxide analyses, since both meters were to some extent sensitive to carbon dioxide in the amount present in alveolar air. Great care was taken with both meters to check the deflection to known gas mixtures with each analysis. The stability of calibration was checked every few months and varied only within narrow limits during the 1 year period in which both initial and follow-up studies were performed.

The test gas consisted of 12.05-12.70 per cent helium, 0.308-0.492 per cent carbon monoxide, 20 per cent oxygen and the remainder nitrogen. The variation in inspired carbon monoxide concentration was greater than desired; however, this appeared to have no effect on DL_{CO} as judged by determinations in a normal subject, where both the higher and lower concentrations were used at the same sitting.

In preliminary experiments, determination of the resting diffusing capacity by the steady-state method of Filley, MacIntosh and Wright[10] was accomplished in 5 of the cases of IASD, 2 cases of IVSD, and 1 case of rheumatic heart disease. In our hands this technic gave erratic results in resting subjects. This was thought to be caused by difficulty in obtaining the extreme accuracy of $P_{A_{CO_2}}$ determination necessary for the estimation of the mean diffusion gradient. Those data that were obtained suggested that the $P_{A_{CO_2}}$ determination is even more critical where the diffusing capacity at rest is increased, inasmuch as part of the effect of an augmented DL in a resting subject may be to reduce the mean value of the diffusion gradient. As a result of these practical and theoretical considerations the method was abandoned in the present study, and the data are not reported.

In 15 patients the interval between DL_{CO} determinations and catheterization studies was less than 6 months. In 3 patients an interval of more than 2 years separated the 2 studies. However, clinical findings failed in any case to suggest a degree of change that would have invalidated correlation of the data from the different procedures.

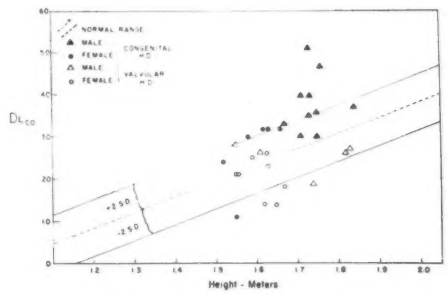


FIG. 1. Relationship between single-breath diffusing capacity and body height. Normal range and standard deviation determined in 19 control subjects are shown by the *parallel lines*.

Maximum ventilatory capacity was determined with a modified 9 liter spirometer. Predicted values for the maximum ventilatory capacity were derived from the formula of Baldwin et al.[11] Predicted values for lung volumes in seated, nonfasting subjects were derived from the data of Needham et al.,[12] a factor of 1.06 being used to raise the figures of ambient temperature and pressure saturated with water vapor to those of body temperature.

RESULTS

In the 19 normal subjects (table 3) a significant correlation was found between DL_{CO} and body height (DL_{CO} = 37.4 × body height (M.) − 36.5; S.D. = ± 3.25 ml./min./mm. Hg; r = 0.71). For all normal subjects and for patients a predicted value was computed from this formula, from which the percentage ratio, DL_{CO} observed/DL_{CO} predicted × 100, was derived. The mean of these values for the normal subjects was 100 per cent with a standard deviation of ± 12.5 per cent and range of 85 to 127 per cent. Values differing by more than 6.5 ml./min./mm. Hg from predicted are considered to be elevated or reduced, inasmuch as they fall outside of the 95 per cent confidence limits established by the normal series.

By these criteria, 10 of the 16 patients with congenital heart disease had elevated values of DL_{CO_2} and 1 patient had a reduced value (table 2). In 5 patients the test was normal.

TABLE 3.—*Normal Subjects; Lung Volumes and Diffusing Capacity*

Case No.	Age	Sex	Ht. (cm.)	BSA ($M.^2$)	Vital capacity (L.) obs.	Vital capacity (L.) % pred.	Residual volume/ total lung capacity (%)	Mixing index (% N_2)	Max. breathing capacity (L./min.) obs.	Max. breathing capacity (L./min.) % pred.	DL_{CO} obs. (ml./ min./ mm. Hg)	DL_{CO} pred. (ml./ min./ mm. Hg)	DL_{CO} % pred.
30	16	M	180	1.93	5730	110	10	0.71	138	91	33	31	106
31	17	M	165	1.73	3870	87	16	0.57	147	110	31	25	124
32	27	M	176	1.99	4680	92	21	1.08	126	88	35	29	121
33	30	M	194	2.29	6260	109	19	0.59	150	92	33	36	92
34	32	M	180	1.95	5950	117	25	0.70	217	160	33	31	106
35	35	M	183	2.05	6160	122	24	0.76	185	132	31	32	97
36	35	M	170	1.76	5580	124	23	1.29	127	106	23	27	85
37	45	M	180	1.94	5230	114	27	0.99	158	128	29	31	94
38	55	M	175	1.99	3830	96	35	0.92	123	107	28	29	97
39	65	M	167	1.70	3700	115	38	1.71	95	107	25	26	96
40	74	M	153	1.53	3180	149	42	1.79	68	93	19	21	90
41	19	F	158	1.50	3350	107	24	0.49	114	123	25	23	109
42	24	F	162	1.51	3140	93	28	0.75	109	121	23	24	96
43	26	F	166	1.64	3570	102	19	0.62	136	142	23	26	88
44	26	F	164	1.59	3840	113	27	0.49	98	103	25	25	100
45	27	F	156	1.58	3440	111	26	0.48	121	130	28	22	127
46	50	F	158	1.74	2160	82	36	0.63	133	160	20	22	91
47	51	F	160	1.61	2520	92	30	1.09	79	104	23	23	100
48	55	F	152	1.43	2500	108	37	1.14	71	109	17	20	85
Average	37	—	168	1.76	4142	108	27	0.88	126	116	27	26	100
Range	16-74		152-194	1.43-2.29	2160-6260	82-149	10-42	0.48-1.79	68-217	88-160	17-35	20-36	85-127

In the group with rheumatic heart disease, the values were normal in 9 patients and reduced in 4 (fig. 1).

Because both patient groups contained individuals with disease processes of greatly differing degrees of severity, 3 graphs are presented in which DL_{CO} as percentage of predicted value is plotted against various parameters (figs. 2-4). Thus, if allowance is made for differences in clinical severity (fig. 2), in the vital capacity measurement (fig. 3), and in the level of pulmonary artery pressure (fig. 4), patients with intracardiac septal defects tend to have higher values for diffusing capacity than patients with rheumatic heart dis ease.

Figure 5 relates the resting pulmonary bood flow to DL_{CO}. Resting pulmonary blood flow was normal or reduced in all the rheumatic subjects and was elevated in all but 4 of the 16 congenital patients. No instances of an elevated DL_{CO} in the presence of a reduced value for pulmonary blood flow were encountered, and, conversely, no reduced values for DL_{CO} were found in patients with elevated pulmonary blood flows.

The results of serial determinations of DL_{CO} are presented in figures 6 and 7. In the normal subjects followed over a 1 year period, the largest change between any 2 values expressed as a percentage of the greater value was 21 per cent. This could well be a summation of technical errors, inasmuch as variations of a similar magnitude would occasionally occur at a single sitting. The average variation at a single sitting, however, was 7 per cent.

Serial determinations were also performed in 4 patients with congenital heart disease and in 4 patients with rheumatic valvular heart disease. The normal degree of variation was exceeded in only 1 case (R.A., case 5), in whom a fall of 27 per cent from the original value of DL_{CO} occurred prior to corrective surgery, with a subsequent further fall postoperatively. In figure 7 this is expressed as

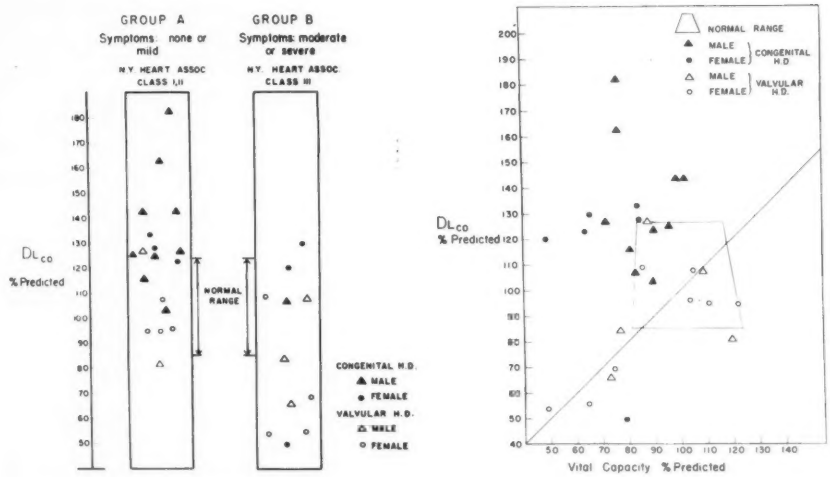


FIG. 2 *Left.* Single-breath diffusing capacity in congenital and rheumatic heart disease with patients grouped according to clinical severity. Single-breath diffusing capacity is expressed as a percentage of the predicted value.

FIG. 3 *Right.* Relationship between single-breath diffusing capacity and vital capacity. Both vital capacity and DL_{CO} are expressed as percentage of predicted. Values on all 19 normal subjects fell within the trapezoid. *Diagonal line* is line of identity.

a fall from 179 per cent of the predicted figure to a final value of 107 per cent of predicted. This patient had an ostium secundum type of IASD with pulmonary artery pressure of 35/12 and a pulmonary blood flow of 19 L./min./M.^{2} BSA at the time of the original examination. During the ensuing 9 months he noted increased fatigability and was found at a second catheterization to have an unchanged value of pulmonary artery pressure; the pulmonary blood flow was found to be 11 L./min./M.^{2} BSA, but this change is of questionable significance. Satisfactory closure of the defect was accomplished, and the final measurement of DL_{CO} was made when he was in a symptomatically improved state.

In another patient with IASD (A.A. case 8) a significantly elevated DL_{CO} fell to normal postoperatively, and in 1 case of mitral stenosis (R.L., case 27) a rise of 17 per cent occurred after a successful valvuloplasty. In 3 other cases of mitral stenosis the values fell insignificantly or were unchanged. These 3 valvuloplasties were at least partially successful both from the technical standpoint and from the evaluation of symptoms in the early months of follow-up.

DISCUSSION

This study indicates that elevation of the resting diffusing capacity is probably a common occurrence in patients with intracardiac septal defects. Although this observation cannot be clearly correlated with any single associated finding in the other tests performed, the data suggest that the level of pulmonary blood flow is of major importance. This conclusion is based principally on the grouping of points in figure 5. The degree of scatter of these points is considerable, but such scatter is to be expected if the number of causes of biologic variation and technical error are considered. In particular, the estimation of pulmonary blood flow at rest by the Fick technic is inaccurate when the flow is markedly increased.

Recent work by Roughton and Forster[6] strongly indicates that the value of DL_{CO} is

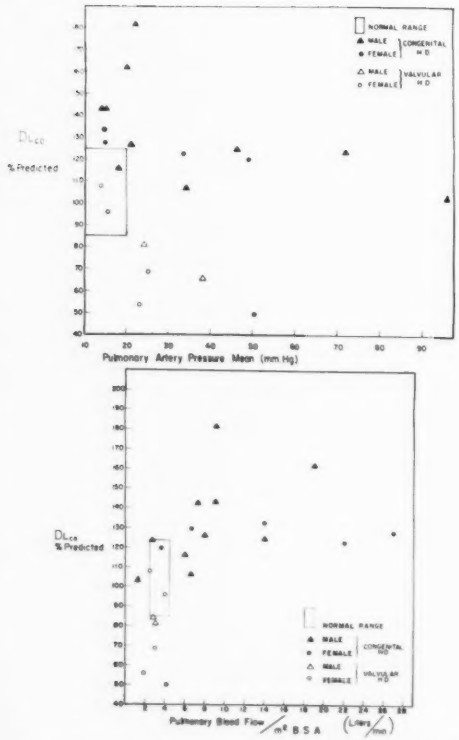


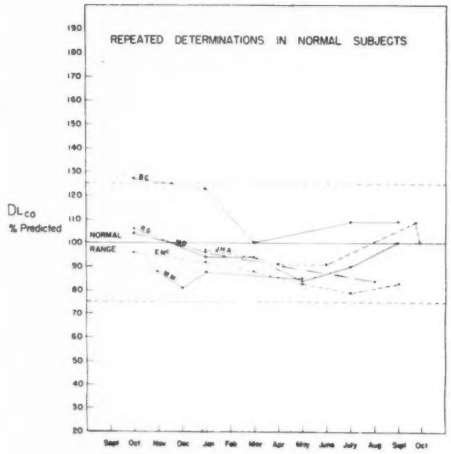
FIG. 4 *Top.* Relationship between single-breath diffusing capacity and mean pulmonary artery pressure.

FIG. 5 *Bottom.* Relationship between single-breath diffusing capacity and pulmonary blood flow. Diffusing capacity was elevated only in the presence of increased pulmonary blood flow, and was never below normal when pulmonary blood flow was high.

affected not only by the resistance offered by the pulmonary membrane to gas diffusion but also by resistance encountered by the CO molecule in its passage across the red-cell membrane and into chemical union with hemoglobin. This latter resistance is reduced as the capillary blood volume increases. It is impossible from the present data to demonstrate that the increased value for DL_{CO} represents only a functional expansion of the alveolo-capillary membrane as opposed to an increase in capillary blood volume. In fact, under conditions of increased pulmonary blood flow it seems unlikely that either type of change could occur without the other.

Whatever the change in the pulmonary capillary circulation may be in patients with uncomplicated shunts, the conditions are likely to be similar to those present in vigorous exercise in normal subjects. Under both circumstances large pulmonary blood flows are tolerated with no, or minimal, rises in pulmonary artery pressure. If it be assumed that in all of our patients with septal defect this uncomplicated condition existed at one time, it can be concluded that the finding of a normal diffusing capacity in the presence of pulmonary hypertension (fig. 4) represents a fall from a previously elevated value. Our data do not determine whether this fall in DL_{CO} is primarily related to the decrease in pulmonary blood flow or to damage to the alveolo-capillary membrane related to the process of vascular obstruction. Edwards[13] has described cellular fibrous intimal thickening in small pulmonary arteries and arterioles in pathologic material from patients with IASD and moderate pulmonary hypertension. These lesions may be completely occlusive but are focal; because of this fact it seems likely that areas of lung are functionally removed from the process of gas exchange, while in other areas the capillary bed is fully expanded. With severe pulmonary hypertension the occlusive lesions were present in vessels as wide as 300 microns. Presumably, once initiated, this process of focal vascular occlusion progresses, and its severity must therefore be related to its duration. Such considerations render more plausible some of the individual values of DL_{CO} obtained. For example, both cases 10 and 16 had marked pulmonary hypertension with normal values for pulmonary blood flow. In case 10, a 20 year old male, DL_{CO} was elevated, while in case 16, a 47 year old woman, it was markedly reduced.

In this study, DL_{CO} in mitral valve disease was normal or reduced; similar results for DL_{O2} were obtained by Carroll, Cohn, and Riley.[5] It is thus obvious that active hyperemia, as exemplified by IASD, and passive congestion caused by valvular heart disease do not have identical effects on the pulmonary


REPEATED DETERMINATIONS IN NORMAL SUBJECTS
DL-CO % Predicted
NORMAL RANGE
Sept Oct Nov Dec Jan Feb Mar Apr May June July Aug Sept Oct

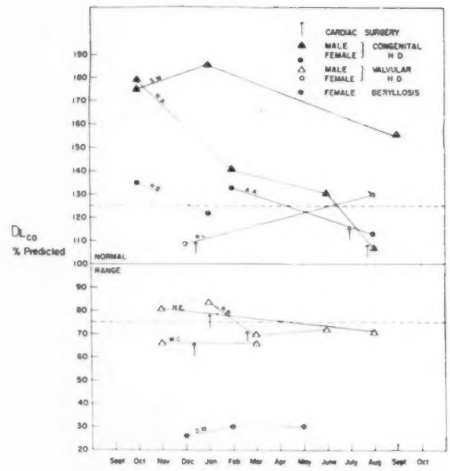


FIG. 6 *Top.* Variations in single-breath diffusing capacity in normal subjects studied over 1 year.

FIG. 7 *Bottom.* Variations in single-breath diffusing capacity in patients with congenital and rheumatic heart disease studied over 1 year. Time of corrective cardiac surgery is indicated by the *vertical arrows.*

capillary bed. It may be that while both conditions produce capillary dilatation, associated effects of pulmonary congestion cause a reduction in diffusing capacity. These associated effects in advanced cases have been well described by Parker and Weiss[14] and are not limited to the pulmonary capillary. Fibrosis of the interstitium, thickening of the alveolar membrane, and edema (both interstitial and intra-alveolar) collectively provide ample explanation of the reduction in diffusing capacity that occurs in advanced cases. This knowledge, plus the failure of DL_{CO} to rise in 3 of 4 cases studied after valvuloplasty, suggest that a reduced DL_{CO} in mitral valve disease may be an indication of permanent damage to the lung parenchyma, rather than simply the result of congestion or diminished pulmonary blood flow.

It is not proposed that a single determination of DL_{CO} materially improves the evaluation of the individual patient with intracardiac septal defect. It would, however, appear to have possible use when serially determined. If such determinations show a significant fall from an initially elevated value, it becomes difficult to escape the conclusion that progressive deterioration is occurring in the pulmonary circulation. The symptomatic and clinical evidences of these changes are by no means clear-cut, particularly in the early stages. There would appear, therefore, to be potential usefulness in a safe, reproducible procedure that correlates with events taking place in the pulmonary capillary bed.

SUMMARY

The pulmonary diffusing capacity was determined by the single-breadth carbon monoxide technic in 16 patients with intracardiac septal defects, 13 patients with rheumatic valvular heart disease, and 19 normal subjects. Significantly elevated values were found in 10 patients with intracardiac septal defects, in 9 of whom the pulmonary blood flow was elevated. Normal or insignificantly elevated values usually occurred where intracardiac septal defects were accompanied by moderate or marked degrees of pulmonary hypertension. A significantly reduced value was obtained in 1 patient with interatrial septal defect complicated by marked pulmonary hypertension and in 4 of the 13 subjects with rheumatic valvular heart disease. In 2 subjects with interatrial septal defect the diffusing capacity was initially elevated but became normal following closure of the defect. The data

are consistent with the concepts that pulmonary blood flow and diffusing capacity are related quantities and that the pulmonary vascular complications in patients with intracardiac septal defects may also cause impaired diffusion by a more direct mechanism in some cases. In view of these considerations, serial determinations of diffusing capacity may have clinical value in prognosis and in determining the urgency of the need for corrective surgery.

Acknowledgment

We wish to express our thanks to Miss Elizabeth Coulter, Mrs. Mary Burdick, and Miss Eileen McAuliffe for their technical assistance.

Summario in Interlingua

Le capacitate pulmonar de diffusion esseva determinate per medio del technica a inspiration unic de monoxydo de carbon in 16 patientes con defectos de septo intracardiac, 13 patientes con rheumatic morbo de valvula cardiac, e 19 subjectos normal. Valores significativemente elevate esseva trovate in 10 patientes con defectos de septo intracardiac, incluse 9 in qui le fluxo de sanguine pulmonar esseva elevate. Valores normal o insignificativemente elevate occurreva usualmente in casos in que defectos de septo intracardiac esseva accompaniate de grados moderate o marcate de hypertension pulmonar. Un significativemente reducite valor esseva obtenite in 1 patiente con defecto de septo interatrial complicate per marcate grados de hypertension pulmonar e in 4 ex 13 subjectos con morbo rheumatic de valvula cardiac. In 2 subjectos con defectos de septo interatrial, le capacitate diffusori esseva initialmente elevate sed deveniva normal post que le defecto habeva essite claudite. Le datos es compatibile con le conception que le fluxo de sanguine pulmonar e le capacitate diffusori es magnitudes interrelationate e que le complicationes pulmono-vascular in patientes con defectos de septo intracardiac es etiam capace, in certe casos, a causar un compromisso del diffusion per un mechanismo plus directe. Iste considerationes suggere que determinationes serial del capacitate diffusori es possibilemente de valor clinic in establir le prognose e in determinar le urgentia de chirurgia corrective in le caso individual.

References

1. Forster, R. E., Cohn, J. E., Briscoe, W. A., Blakemore, W. S., and Riley, R. L.: A modification of the Krogh carbon monoxide breath holding technique for estimating the diffusing capacity of the lung; a comparison with three other methods. J. Clin. Invest. **34**: 1417, 1955.
2. Austrian, R., McClement, J. H., Renzetti, A. D., Jr., Donald, K. W., Riley, R. L., and Cournand, A.: Clinical and physiological features of some types of pulmonary diseases with impairment of alveolar-capillary diffusion. The syndrome of "alveolar-capillary block." Am. J. Med. **11**: 667, 1951.
3. Shepard, R. H., Cohn, J. E., Cohen, G., Armstrong, B. W., Carroll, D. G., Donoso, H., and Riley, R. L.: The maximal diffusing capacity of the lung in chronic obstructive disease of the airways. Am. Rev. Tubere. **71**: 249, 1955.
4. Bates, D. V., Knott, J. M. S., and Christie, R. V.: Respiratory function in emphysema in relation to prognosis. Quart. J. Med. **25**: 137, 1956.
5. Carroll, D., Cohn, J. E., and Riley, R. L.: Pulmonary function in mitral valvular disease: distribution and diffusion characteristics in resting patients. J. Clin. Invest. **32**: 510, 1953.
6. Roughton, F. J. W., and Forster, R. E.: Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J. Appl. Physiol. **11**: 290, 1957.
7. Auchincloss, J. H., Jr., and Duggan, J. J.: Effects of venesection on pulmonary and cardiac function in patients with chronic pulmonary emphysema and secondary polycythemia. Am. J. Med. **22**: 74, 1957.
8. Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W.: A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. J. Clin. Invest. **36**: 1, 1957.
9. Darling, R. C., Cournand, A., and Richards, D. W., Jr.: Studies on the intrapulmonary mixture of gases. III. An open circuit

method for measuring residual air. J. Clin. Invest. **19**: 609, 1940.

10. Filley, G. F., MacIntosh, D. J., and Wright, G. W.: Carbon monoxide uptake and pulmonary diffusing capacity in normal subjects at rest and during exercise. J. Clin. Invest. **33**: 530, 1954.
11. Baldwin, E. de F., Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine **27**: 243, 1948.
12. Needham, C. D., Rogan, M. C., and McDonald, I.: Normal standards for lung volumes, intrapulmonary gas-mixing, and maximum breathing capacity. Thorax **9**: 313, 1954.
13. Edwards, J. E.: Functional pathology of the pulmonary vascular tree in congenital cardiac disease. Circulation **15**: 164, 1957.
14. Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12**: 573, 1936.

Dahl, L. K., and Love, R. A.: Etiological Role of Sodium Chloride Intake in Essential Hypertension in Humans. J.A.M.A. **164**: 397 (May 25), 1957.

The 1,346 persons working at the Brookhaven National Laboratory since 1953 were classified by history and physical examination with the following results. The average age was 34.6 years (±10.0) and five sixths were males. The 135 individuals who denied ever adding sodium chloride to their food had an incidence of hypertension (140 mm. Hg systolic, 90 mm. Hg diastolic or higher) of 0.7 per cent. In contrast, 10.5 per cent hypertensive individuals were found in the group of 581 individuals who routinely added salt to food before tasting it. The incidence of hypertension in the high salt group as compared with the low salt group was greater in non-overweight persons and much greater in overweight persons. The distinction by history between the low- and high-salt-intake groups was validated by the results of urine sodium analyses done in a number of cases. It was proposed that the level of sodium intake is the primary etiologic factor in the development of essential hypertension.

Rogers

Familial Pseudoxanthoma Elasticum and Valvular Heart Disease

By JAY D. COFFMAN, M.D., AND SHELDON C. SOMMERS, M.D.

The clinical and pathologic findings are presented of a patient with pseudoxanthoma elasticum leading to fatal valvular heart disease. The literature concerning the involvement of the heart by this disease is reviewed and reveals that valvular heart disease has not been described as a clinical problem heretofore. The occurrence of the condition in the relatives of the patient is described.

PSEUDOXANTHOMA ELASTICUM has been described as a systemic disease that affects the skin, the eyes, and the blood vessels. That it may directly involve the heart and cause significant valvular disease is not so well known. Histologic changes in the endocardium and heart valves have been described[1-3] but valvular heart disease has not been a clinical problem in these cases. After studying the following familial cases of pseudoxanthoma elasticum, especially case 1 who died in severe congestive heart failure due to mitral stenosis, it was considered that another differential diagnosis must be added to the uncommon causes of valvular heart disease.

Case 1. Mrs. M. K. (MMH 390-037), a 68-year-old white housewife of Portuguese extraction, entered the Massachusetts Memorial Hospitals because of shortness of breath. Three years prior to admission she developed irregular heart action and symptoms of congestive heart failure that were controlled by digitalis and diuretics. During the previous month she became dyspneic and was confined to bed, the legs and abdomen became swollen, and the urinary output decreased. She denied chest pain or knowledge of high blood pressure.

Past history included an attack of "influenza" in 1918, following which a heart murmur was heard. There were no other episodes suggestive of rheumatic fever.

Physical examination revealed an obese dyspneic woman. The temperature was 101 F., and respirations were 30; the blood pressure was 140 mm. Hg systolic and 80 diastolic. The skin was pale, loose, dry, and sealy, with large ecchymoses on the forearms. The neck veins were distended. There were fine rales over the left lower lung field posteriorly. Cardiac dullness extended from the left anterior axillary line to 3 cm. to the right of the sternal border in the fifth interspace. The rhythm was grossly irregular. The first heart sound was accentuated and an opening snap was heard. A grade-II, low-pitched, rumbling mid-diastolic murmur was localized to the apex. A grade-III, rough, blowing systolic murmur was loudest at the apex and radiated to the axilla. The pulmonic component of the second heart sound was louder than the aortic. A fluid wave and shifting dullness were noted in the abdomen. The liver was firm, nontender, and pulsating 5 cm. below the right costal margin. There was pitting edema of the entire lower extremities.

The hemoglobin was 6.3 Gm. per 100 ml. and the hematocrit level was 22 per cent; the red blood cell count was 2.76 million per mm.^{3} The icteric index was 5. The serum sodium was 143 mEq., the potassium 5.3 mEq., the chloride 110 mEq., and the carbon dioxide 19.8 mEq. per liter. The fasting blood sugar was 121 mg., the total protein 6.1 Gm., the albumin 3.8 Gm., and the globulin 2.3 Gm. per 100 ml. The protein-bound iodine was 4.2 μg., the total iodine 4.2 μg., and the serum iron 9 μg. per 100 ml. Urinalysis was negative except for 1+ albumin.

A chest x-ray film showed a markedly enlarged heart with a contour suggesting pericardial effusion. An electrocardiogram revealed atrial fibrillation with a ventricular rate of 90, occasional ventricular premature beats, right axis deviation, and ST-T abnormalities attributed to digitalis.

The morning after admission, the patient suddenly became very dyspneic, vomited a small amount of material, and died.

Gross and microscopic findings of the autopsy showed unusual changes in the heart, kidney, and blood vessels. The abdominal cavity contained about 2,000 ml. and the pericardial cavity 200 ml. of serous fluid. The empty heart weighed 750 Gm.; there was hypertrophy, mostly of the left ventricle, and dilatation of all chambers. The left

From the Departments of Medicine and Pathology, Boston University School of Medicine, and Massachusetts Memorial Hospitals, Boston, Mass.

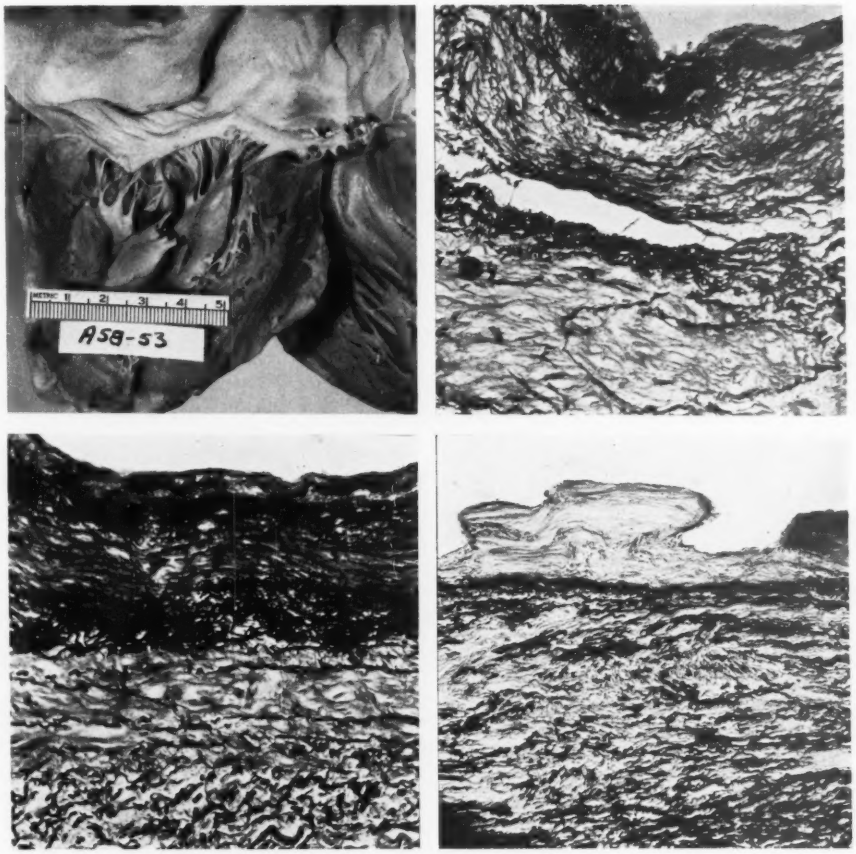


FIG. 1 *Top left.* Opened heart of case 1, showing the wrinkled left atrium, rolled thickened mitral valve cusps with calcification at the right, and a yellow discolored atrial area just above the calcifications. The chordae tendineae appear normal.

FIG. 2 *Bottom left.* Left atrium, with the endocardial surface at the top, stained to show the elastic tissue as black strands. Note that the more superficial elastica is relatively normal, but that the deeper elastic tissue is abnormally fragmented, irregular, coarse-fibered and partly palisaded at right angles to the surface. Verhoeff-van Gieson stain. × 250.

FIG. 3 *Top right.* Mitral valve, demonstrating some black-stained curled, coarse broken elastic fibers below the artefactual lacunar space. Endocardial surface is at the top. Verhoeff-van Gieson stain. × 250.

FIG. 4 *Bottom right.* Aorta, showing the bizarre ridge-like thickenings of the intima, beneath which the black-stained elastic tissue is in disarray, with marked degeneration. Verhoeff-van Gieson stain. × 90.

trium had a wrinkled, white and yellow, opaque ndocardium. The mitral valve was narrowed and ish-mouthed in appearance, with thickening and ocalized calcification at the leaflet margins. The hordae tendineae were normal (fig. 1). The other ardiae valves and coronary arteries were within ormal limits for the patient's age. Microscopically, the heart valves, including the mitral valve, were not vascularized and there was endocardial and valvular thickening by dense connective tissue. No inflammation or Aschoff bodies were observed.

Special stains for elastic tissue showed that the elastic fibers in the thickened endocardium were abnormally increased in number, coarse, fragmented, and locally palisaded perpendicular to the surface (fig. 2). In the mitral valve, and to a

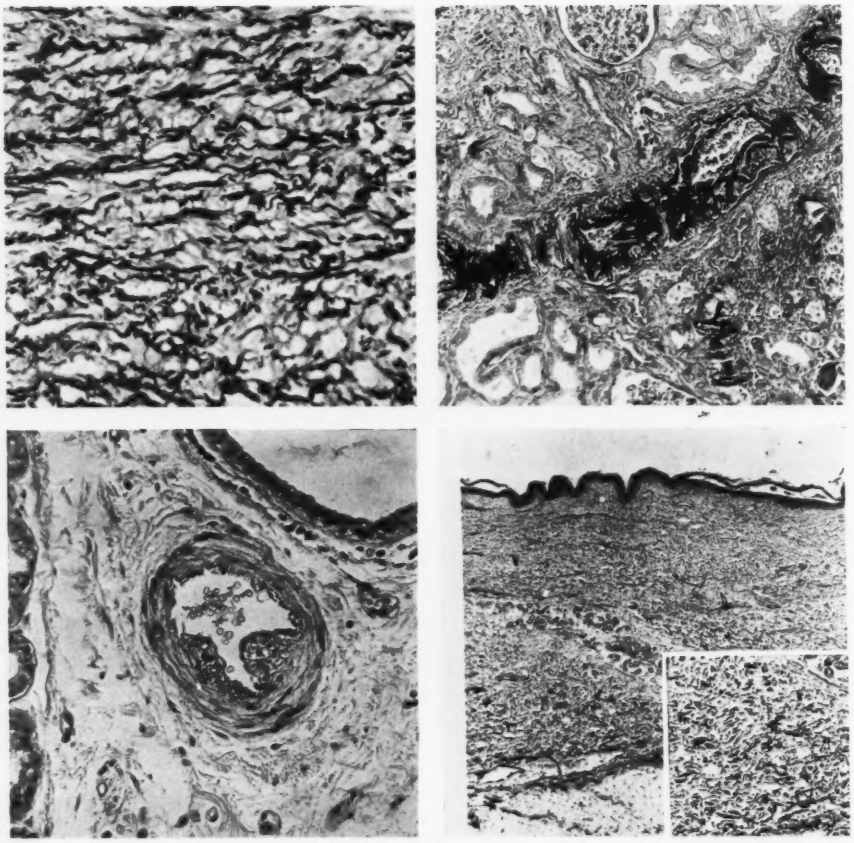


FIG. 5 *Top left.* Aortic media at higher magnification showing extremely peculiar alterations of black-stained elastic fibers and hydropic degeneration of the intervening gray-stained muscle. Verhoeff-van Gieson stain. × 250.

FIG. 6 *Bottom left.* Small artery in the gastric submucosa is shown, with nearby accessory glands of the cardia. Marked degeneration of the internal elastic membrane is present. Hematoxylin and eosin stain. × 250.

FIG. 7 *Top right.* Kidney of case 1, with elastic tissue stained black, to illustrate the unusual degenerative changes found in the arterial and arteriolar elastica. Verhoeff-van Gieson stain. × 90.

FIG. 8 *Bottom right.* Skin specimen from case 1. The epidermis is wrinkled, and the black-stained elastic tissue of the upper dermis appears normal. The lower dermis and insert contain coarse degenerated, dermal elastic fibers, curled and broken, typical of pseudoxanthoma elasticum. Verhoeff-van Gieson stain. × 20; insert × 40.

lesser extent in other cardiac valves, the elastic fibers were abnormally coarse, curled, and fragmented (fig. 3). Grossly the aorta and major vessels appeared elastic. Moderate intimal thickening, calcification, and lipoid deposition were present in the abdominal aorta. The ascending aorta had a peculiar transversely wrinkled appearance with a yellow color, more marked along the ridges between the wrinkles. Microscopically, both in aorta and pulmonary artery there were intimal hillocks that contained fine fibers lightly stained by elastic-tissue technic; below this level the elastic tissue of the media was unusually abundant, coarse and fragmented (fig. 4). The muscle of the aortic media appeared hydropic (fig. 5).

The lungs weighed 900 Gm. together, the spleen 500 Gm., and the liver 1,450 Gm.; all showed chronic passive congestion. There were petechial

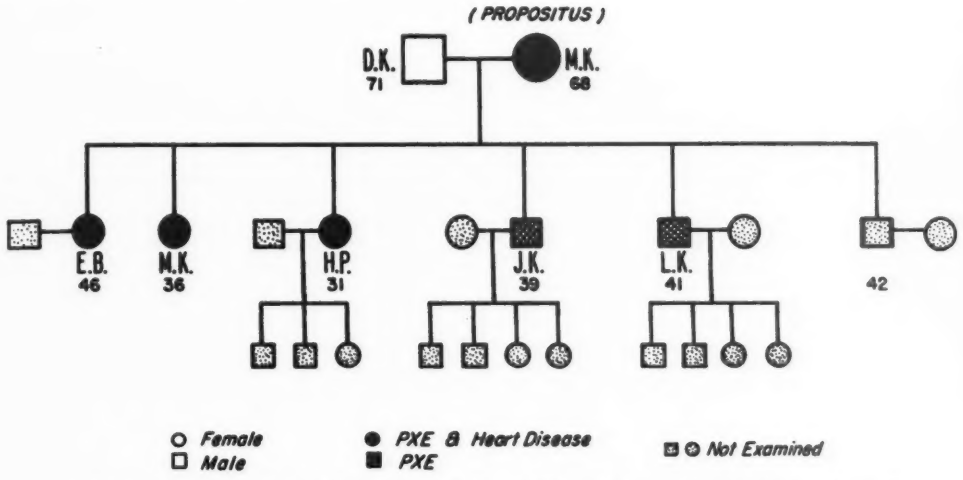


FIG. 9. Pedigree of the family of case 1 (Mrs. M. K.), to demonstrate the relationships and abnormalities observed. Patient's initials and ages in years at the time of examination are given.

hemorrhages in the gastric mucosa, and microscopically occasional small arteries showed extreme thickening and degeneration of the internal elastic lamina, unlike that seen in arteriosclerosis (fig. 6).

Each adrenal gland weighed 9 Gm. and each kidney 150 Gm. The renal capsules stripped with some difficulty, leaving a pitted, diffusely granular, pale tan surface. The cortices were poorly demarcated and measured 0.6 cm. in width. Microscopically there were extreme localized thickening, reduplication and fragmentation of elastic tissue in the small renal arteries and in some arterioles. Glomeruli were large and rather ischemic, with nonspecific sclerotic changes and a slight increase in the number of nuclei. Focal interstitial chronic inflammation was seen, consistent with pyelonephritis (fig. 7).

Grossly the skin appeared wrinkled and pale with induration and brownish discoloration over the legs. Microscopically in the deep corium, with routine stain, the connective tissue appeared abnormally coarse and slightly basophilic. This tissue stained green like collagen with the Masson trichrome method. The elastic-tissue stain showed a striking degeneration of elastic fibers deep in the corium, with fragmentation, coalescence, thickening, and curling of elastic tissue, typical of pseudoxanthoma elasticum (fig. 8).

Incidental findings included cholelithiasis, endometrial hyperplasia, chronic cystic mastitis with intraductal papillomas, ovarian stromal hyperplasia, and cavernous hemangioma of a lumbar vertebra.

Death was attributed to congestive heart failure in the presence of pseudoxanthoma elasticum involving the heart, kidney, aorta, pulmonary artery, small blood vessels, and skin.

Case 2. E. B. (MMH 389-706), a 46-year-old daughter of case 1 (fig. 9) entered the Massachusetts Memorial Hospitals for extraction of teeth. At age 9 she was told by the school physician that she had a heart murmur. She remembered no episode resembling rheumatic fever. No cardiac symptoms were present until exertional dyspnea developed 3 years prior to admission. Two years after this she experienced a transient loss of motor power of the right leg for 1 day. Six months later she developed numbness of the left side of her face and of her left hand. These symptoms gradually improved.

There were no indications of a bleeding tendency from any system; her menstrual history was normal. Symptoms of peripheral vascular disease, except as noted above, were absent. She had had blurred vision in her right eye since birth.

She had had 2 thyroid operations, 14 and 12 years previously, for symptoms of hyperthyroidism and exophthalmos. Ten years prior to admission she was given thyroid medication for "low thyroid activity." She stopped taking it because it made her nervous.

Physical examination revealed a well developed, middle-aged woman in no distress. Pulse was 70 and respirations were 16 per minute. Blood pressure was 110 systolic mm. Hg and 78 diastolic. The skin was dry and of fine texture; a 2 by 3 cm.

atrophic, wrinkled area was present on the lower back. There was marked exophthalmos. The right fundus could not be visualized because of a cataract; the left fundus was normal. The neck veins were distended but the lungs were clear to auscultation and percussion. A grade-III rough blowing systolic murmur was heard loudest at the aortic area and transmitted to the neck and axilla. A grade-II, high-pitched, soft, blowing diastolic murmur was present at the aortic area and in the third left interspace parasternally. The pulmonic component of the second heart sound was louder than the aortic. The rhythm was regular. Pulses below the femorals were absent in the legs; the radial pulses were of normal amplitude. There was weakness of the left facial muscles.

Blood urea nitrogen, fasting sugar, electrolytes, and total protein were normal. A serum cholesterol was 383 mg. per 100 ml. Urinalysis revealed 1+ albumin. The basal metabolic rate was +1 per cent.

Cardiac fluoroscopy showed the heart to be enlarged in all diameters with no specific chamber enlargement. The barium-filled esophagus was displaced posteriorly. There was generalized diminution of cardiac pulsations. The lung fields showed increased prominence of the bronchovascular pattern. An electrocardiogram revealed nonspecific T-wave abnormalities and late U waves, which were inverted over the left precordium.

The patient was given thyroid extract and digitalis, and she improved considerably.

Skin biopsy from the atrophic, wrinkled, lumbar area was diagnosed as pseudoxanthoma elasticum. The deeper layers of dermis appeared abnormally basophilic and were composed of curled heavy connective-tissue strands with the hematoxylin and eosin stain. With Verhoeff-van Gieson stain for elastic tissue, the elastica of the superficial dermis was practically normal, but in the lower dermis the elastic fibers were coarse, broken, curled, and irregular both in distribution and in the appearance of individual fibers.

Case 3. M. K., the second eldest daughter of case 1 who was 36 years of age, was examined for evidence of pseudoxanthoma elasticum. She had been healthy all her life. There were no symptoms of bleeding from any system and her menstrual history was normal. She stated that small ecchymoses of the legs developed very easily. She denied cardiac or peripheral vascular symptoms except for palpitation and a tightness in the anterior chest when nervous. There were no visual difficulties. Past history failed to reveal any episode resembling rheumatic fever.

The fundi and skin were normal. A grade-II, rough, blowing, systolic murmur was heard precordially but loudest in the right supraclavicular fossa; it was not transmitted to the axilla. The aortic component of the second basal heart sound was louder than the pulmonic. The rhythm was regular. The blood pressure was 150/80. This murmur was considered most consistent with aortic stenosis. Peripheral pulses were of normal amplitude.

Chest films and cardiac fluoroscopy showed the heart to be normal in size and contour. There was minimal but normal posterior indentation of the barium-filled esophagus in the region of the atria. No intracardiac calcification was seen. An electrocardiogram showed sinus arrhythmia and prominent U waves.

A skin biopsy showed localized abnormalities of the lower dermis with fragmentation of elastic fibers, consistent with mild pseudoxanthoma elasticum.

Case 4. H. P. (MMH 507-115), a 31-year-old daughter of the patient of case 1 entered the hospital for repair of a hernia. She had had a heart murmur since childhood and was restricted in sports at school. There was no history of an illness resembling rheumatic fever. Symptoms of heart failure were absent. Except for the appearance of small ecchymoses on her legs without known trauma, there was no bleeding tendency. Menstrual history was normal; she had had 4 miscarriages and 3 normal pregnancies. No visual or peripheral vascular symptoms were present.

The fundi and skin were normal except for a small ecchymosis on the right upper arm. The cardiac impulse was very forceful 2 cm. to the left of the midclavicular line in the fifth interspace. A systolic thrill was felt over this area. There was a grade-IV, rough, blowing systolic murmur, loudest at the apex and transmitted to the axilla but not to the neck. The aortic component of the second basal heart sound was louder than the pulmonic. A third heart sound was heard in early diastole at the lower left sternal border. The rhythm was regular at a rate of 72. The blood pressure was 120/68. The findings were considered most consistent with mitral insufficiency. There were many nonpigmented striae on the abdomen and a large right lower quadrant scar with a bulging hernia. A firm, nontender liver was felt 3 cm. below the right costal margin. The right dorsalis pedis pulse was of small amplitude compared to the left.

Laboratory data were normal, including total cholesterol and protein-bound iodine values.

An electrocardiogram revealed ST-T abnormalities in the left precordial leads suggestive of left ventricular hypertrophy. A chest film showed the heart to be above the normal limits in size with a cardiothoracic ratio of 15.5 to 29.5. The pulmonary artery segment and left atrium were prom

nent. Cardiac fluoroscopy showed an indentation on the barium-filled esophagus in the region of the left and right atria. No intracardiac calcifications were seen. Findings were consistent with mitral valvular disease.

As in cases 1 and 2, skin biopsy showed coarse basophilic connective tissue in the deeper corium. With Verhoeff stain, the deep corium was partly composed of heavy, irregular, curled and broken elastic fibrils, considered pseudoxanthoma elasticum.

Case 5. J. K., a 39-year-old son of case 1 was admitted to another hospital at age 29 for paresthesias and weakness of the left extremities. A complete neurologic study including 3 lumbar punctures that showed 10 to 15 lymphocytes, a first-zone colloidal gold curve, and normal protein resulted in a diagnosis of probable multiple sclerosis. A myelogram was unrevealing. He recovered almost completely and had no further episodes.

He was seen at Massachusetts Memorial Hospitals following his mother's death. His history was negative for symptoms of pseudoxanthoma elasticum. Positive physical findings included a scaly rash of the left elbow present for many years, old acne scars of the back and chest, a blood pressure of 164 systolic, 110 diastolic, and arteriovenous nicking and arteriolar tortuosity of the fundic vessels.

A skin biopsy from the lower back showed that the epidermis was mildly hydropic. The dermis appeared negative, except that the deeper corium had a somewhat basophilic coloration with hematoxylin and eosin, and Verhoeff stain showed exaggerated swelling, coalescence, fragmentation, and curling of elastic fibers. Changes were consistent with mild pseudoxanthoma elasticum.

Case 6. L. K., a 41-year-old son of case 1 had no symptoms or physical findings of pseudoxanthoma elasticum. His only positive physical findings were signs indicating a moderate degree of emphysema. Skin biopsy of the lower back showed mild basophilia of collagen fibers deep in the dermis, associated with abnormal swelling and fragmentation of elastic tissue. These degenerative changes were considered consistent with pseudoxanthoma elasticum.

D. K. (MMH 508534), the 71-year-old Irish husband of case 1 had no symptoms or physical findings suggestive of pseudoxanthoma elasticum. A skin biopsy from the lower back was of normal appearance except for atrophic changes attributable to age. No abnormalities of elastic tissue, resembling those described above were identified with the Verhoeff-van Gieson stain.

A third son of case 1 was not available for examination.

Discussion

Pseudoxanthoma elasticum has been the subject of many papers[2, 4–7] reviewing the typical skin appearance and the retinal angioid streaks (Grönblad-Strandberg syndrome), the systemic findings, and the pathologic picture. Revell and Carey have provided the following list of systemic symptoms and signs in order of their frequency: hypertension, inequality and changes in pulses, intermittent claudication or angina, calcification of peripheral vessels, abnormal bleeding into the gastrointestinal tract, uterus, bladder and brain, psychic disturbances, and epilepsy.

Signs and symptoms of heart disease are quite common.[6] Left ventricular hypertrophy associated with hypertension and angina pectoris due to coronary arterial involvement by the disease are often present. Pathologic changes in the heart due to pseudoxanthoma elasticum have rarely been encountered. The opinion has been expressed that involvement of the heart would not be expected, since it contains only a small amount of elastic tissue.[4] In his original description of this disease in a 49-year-old man without evidence of clinical heart disease, Balzer[1] described a whitish yellow surface over the greater part of the endocardium of the right atrium as well as plaques of the same color on the ventricular trabeculae and pericardium. Histologically, degeneration of the elastic elements, the same pathologic picture as seen in the corium of the skin, was present at these sites.

McKusick[2] described interesting findings at postmortem examination in a case of pseudoxanthoma elasticum with a loud blowing apical systolic murmur as the only manifestation of heart disease. The heart was not enlarged, weighing 325 Gm. There was a yellowish thickening of the endocardium of the right atrium and a nodular thickening over the trabecular ridges. The posterior leaflet of the tricuspid valve had a smooth, thickened, firm, rolled edge without excrescences. The aortic leaflet of the mitral valve was similarly thickened at the edge and there was marked calcific change at its attachment. Histologically the subendocardial tissue of the right atrium

showed the same changes as described in the skin of pseudoxanthoma elasticum.

Reiner[3] presented the case of a 27-year-old woman with pseudoxanthoma elasticum at the New England Society of Pathologists in 1955. The only cardiac symptom was palpitation. At autopsy the endocardium of the right and left atria and the left ventricle was dull, thickened, and opaque. The histologic picture of the endocardium was typical of pseudoxanthoma elasticum.

Clinically our first patient was believed to have rheumatic heart disease with mitral stenosis and tricuspid insufficiency. Histologically, changes of pseudoxanthoma elasticum were present in the skin, blood vessels, kidney, and heart. The endocardium of the left atrium was thickened and whitish yellow in color. The mitral valve had a hard, rolled ridge along the closure line and was definitely stenotic. Microscopic studies revealed far-advanced degeneration of the elastic fibers in the endocardium. Lack of vascularization of the valves, the normal chordae tendineae, and absence of Aschoff bodies ruled against this being inactive rheumatic heart disease. The patient had shown no obvious skin changes except for the subcutaneous hemorrhages that have also been described in pseudoxanthoma elasticum.[8] The eyegrounds were not visualized, so we cannot say if angioid streaks were present in case 1, but the patient had no history of visual difficulties.

Other patients with pseudoxanthoma elasticum have been described as having heart disease, but histologic proof that this disease involved the elastic tissue of the heart was lacking. Prick[9] presented a 48-year-old woman with pseudoxanthoma elasticum, whose heart was hypertrophied at autopsy. The mitral valve presented a thickened edge with some yellowish white patches, but microscopically only fatty infiltration of the heart muscle was described. This patient had dyspnea on exertion, an enlarged heart with a faint systolic precordial murmur, and an accentuated second aortic heart sound. Von Trannenhain[10] reported a case of pseudoxanthoma elasticum in which the postmortem diagnosis included chronic mitral endocarditis and chronic myocarditis, but histologic studies of the heart were not presented. Small yellowish white deposits were found on the aortic and mitral valves in 1 other case,[4] but microscopic study was again lacking. Systolic murmurs have been heard frequently in patients with pseudoxanthoma elasticum and there has been 1 reported case[11] with the murmur of mitral stenosis.

Five of the 6 children of the patient of case 1 showed the changes of pseudoxanthoma elasticum in skin biopsy, and 3 presented evidence of heart disease (fig. 9). There were no clinical skin lesions in these patients except for an atrophic area of skin in case 2 and an elbow rash in case 5. The history of ecchymosis formation without provocation in the daughters was suggestive. It is not unusual to find the pathologic changes of this disease in normal-appearing skin.[7, 15]

Each of the daughters also had clinically significant heart findings, and there was no history of rheumatic fever. It has been found that about 60 to 70 per cent of those with rheumatic heart disease will have had a known episode of rheumatic fever, if carefully questioned.[12] Whether the heart lesions in the daughters are the result of pseudoxanthoma elasticum cannot be said at this time. In case 2 thyroidectomy had been performed for thyrotoxicosis, which has been believed to have some relationship to pseudoxanthoma elasticum.[6] This daughter also had absent peripheral pulses in the legs. One of the sons had an elevated blood pressure, a common accompaniment of this disease.

Inheritance of pseudoxanthoma elasticum is usually as an autosomal recessive, but rarely is it transmitted as a dominant.[2, 4, 13] Parental consanguinity is common in the latter case. Microscopic study of the skin from 5 of the 6 children of case 1 revealed changes consistent with pseudoxanthoma elasticum. The patient and her husband were of different racial backgrounds and a skin biopsy from the husband failed to reveal evidence of pseudoxanthoma elasticum. McKusick[2] was able to find only 8 cases of direct transmission of

this disease in his survey of the literature; however, it has been rare that skin biopsies were examined from offspring who did not show evident clinical manifestations of the disease. Perhaps when more such studies are performed, the dominant mode of transmission will be found in pedigree studies, as has already been postulated by Weidman, Anderson, and Ayres.[14]

This paper does not pretend to review the controversy regarding the basic lesion of this disease, whether it is really an elastic or a connective tissue degeneration, except to point out that the most recent analytic work with histochemistry, electron microscopy, and enzymes seems to indicate a primary elastic tissue disorder.[7, 15, 16]

Summary

The clinical and postmortem findings in a patient with pseudoxanthoma elasticum, who died in congestive heart failure due to mitral stenosis, are presented. Histologic examination of the heart revealed elastic-tissue degeneration in the endocardium of the left atrium and in the valves and no evidence for rheumatic heart disease. The skin, blood vessel, and kidney sections also showed the changes of pseudoxanthoma elasticum.

Five of the patient's 6 children were available for skin biopsies, and all demonstrated some degree of elastic-tissue change consistent with pseudoxanthoma elasticum. Three of the children also had evidence of valvular heart disease. A skin biopsy from the patient's husband was normal, indicating a dominant mode of inheritance, which has been considered rare.

In the 3 previously reported cases of pseudoxanthoma elasticum with histologic cardiac involvement, valvular heart disease was not a clinical problem. It is thought that pseudoxanthoma elasticum must be added to the list of uncommon causes of valvular heart disease. When a patient with the findings of valvular heart disease lacks a history of rheumatic fever, pseudoxanthoma elasticum should be considered.

Summario in Interlingua

Es presentate le constatationes clinic e necroptic in un patiente con pseudoxanthoma elastic, qui moriva in congestive disfallimento cardiac causate per stenosis mitral. Le examine histologic del corde revelava degeneration de histo elastic in le endocardio del atrio sinistre e in le valvulas. Esseva trovate nulle signo de rheumatic morbo cardiac. Le alterationes characteristic de pseudoxanthoma elastic esseva etiam presente in le pelle, le vasos faint systolic precordial murmur, and an acsanguinee, e sectiones renal.

Le patiente habeva 6 filios. Cinque de illes esseva disponibile pro biopsias cutanee, e omne istes monstrava un certe grado de alteration del histos elastic, de character compatibile con un diagnose de pseudoxanthoma elastic. Tres de illes habeva etiam signos de morbo de valvula cardiac. Un biopsia cutanee ab le sposo del patiente esseva normal. Isto indica que le transmission representava le modo dominante, un phenomeno que ha essite considerate como rar.

In le 3 previemente reportate casos de pseudoxanthoma elastic con affection histologic del corde, morbo de valvula cardiac non esseva un problema clinic. Es opinate que pseudoxanthoma elastic debe esser addite al lista del causas incommun de morbo de valvula cardiac. Quando un patiente con indicios de morbo de valvula cardiac es sin historia de febre rheumatic, le possibilitate de pseudoxanthoma elastic deberea esser prendite in consideration.

REFERENCES

1. Balzer, F.: Recherches sur les caractères anatomiques du xanthelasma. Arch. physiol. norm et. path. 4: (series 3) 64, 1884.
2. McKusick, V. A.: Heritable disorders of connective tissue. VI. Pseudoxanthoma elasticum. J. Chron. Dis. 3: 263, 1956.
3. Reiner, L.: Slide Seminar of the New England Society of Pathologists. Jan. 20, 1955.
4. Carlborg, U.: Studies of circulatory disturbances, pulse wave velocity and pressure pulses in larger arteries in cases of pseudoxanthoma elasticum and angioid streaks. Acta med. scandinav. Suppl. 151: 1, 1944.

5. Revell, S. T. R., Jr., and Carey, T. N.: Pseudoxanthoma elasticum as a disseminated disease. South. M. J. **41**: 782, 1948.
6. Szymanski, F. J., and Caro, M. R.: Pseudoxanthoma elasticum: Review of its relationship to internal diseases and report of an unusual case. Arch. Dermat. & Syph. **71**: 184, 1955.
7. Loria, P. R., Kennedy, C. B., Freeman, J. A., and Hemington, V. M.: Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome). Arch. Dermat. & Syph. **76**: 609, 1957.
8. Foerster, O. H.: Pseudoxanthoma elasticum and associated purpura with angioid streaks. Arch. Dermat. & Syph. **30**: 280, 1934.
9. Prick, J. J. G.: Pontine pseudobulbar-paralyse bei Pseudoxanthoma Elasticum. Eine clinische anatomische Studie. Doctoral treatise, Maastricht, 1938. Cited by Carlborg.[4]
10. von Trannenhain, E. G.: Zur Kenntnis des Pseudoxanthoma Elasticum (Darier) Wien klin. Wchnschr. **14**: 1038, 1901.
11. Böck, J.: Zur Klinik und Anatomie der gefässähnlichen Streifen im Augenhintergrund. Ztschr. J. Augent. **95**: 1, 1938 Cited by Carlborg.[4]
12. White, P. D.: Heart Disease. Ed. 4. New York, Macmillan, 1951.
13. Osborn, R. A., and Olivo, M. A.: Pseudoxanthoma elasticum in mother and daughter Arch. Dermat. & Syph. **63**: 661, 1951.
14. Weidman, F. D., Anderson, N. P., and Ayres, S., Jr.: Juvenile elastoma. Arch Dermat. & Syph. **28**: 182, 1933.
15. Fisher, E. R., Rodnan, G. P., and Lansing A. I.: Identification of the anatomic defec in pseudoxanthoma elasticum. Am. J Path. **34**: 566, 1958.
16. Shaffer, B., Copelan, H. W., and Beerman H.: Pseudoxanthoma elasticum. Arch Dermat. & Syph. **76**: 622, 1957.

Grytting, G., and Salvesen, H. A.: Thyrotoxicosis and Myocardial Infarction. Acta med. scandinav. **157**: 169 (April 18), 1957.

Only 1 instance of myocardial infarction was found among 521 thyrotoxic patients aged 40 years or older seen at the Rikshospitalet in Oslo during the 20 years prior to 1956. This patient was a 46-year-old woman who had had severe angina pectoris for about 2½ years before developing the symptoms of thyrotoxicosis. According to Norwegian Life Insurance statistics, 2 myocardial infarctions would have been expected in a group of this size. Three hundred and seventy-eight of these patients had serum cholesterol measurements averaging 160 mg. per cent, which is significantly lower than the 255 mg. per cent average found in normal persons of the same ages. The 15 autopsied thyrotoxic patients showed less than average coronary and aortic atherosclerosis. The authors suggest that thyrotoxicosis may afford some protection against the development of atherosclerosis.

Rogers

The Electrocardiogram of the South African Bantu

By J. D. Woods, M.B., and W. Laurie, M.D.

Considerable attention has been directed to the "suggested" low incidence of atherosclerosis in the Bantu and its relation to diet and blood lipids. Electrocardiographic abnormalities found in the Bantu have been regarded as unreliable evidence either of the presence or the nature of heart disease in these subjects and hence not inconsistent with the alleged freedom of heart disease in these people. In the present study the authors challenge the validity of such an interpretation of electrocardiographic changes.

THE electrocardiogram has become so well established in diagnosis that no heart examination can be considered complete without its use.[1] The only doubt as to the reliability of this method of diagnosis in the Bantu races has been cast by Grusin,[2] who described tracings, abnormal by accepted standards, in large numbers of sick and healthy individuals of this race. He considered that these changes mimicked those found in myocardial infarction, acute cor pulmonale, acute pericarditis, and left ventricular hypertrophy; these changes were found in 22 per cent of healthy nurses, in 63 per cent of consecutive noncardiac medical admissions, and in 63 per cent of consecutive cardiac admissions. He considered these changes to be functional in origin and suggested that they were due to a persistence of the juvenile pattern or to some effect of malnutrition. Whatever the cause of these abnormalities, their occurrence on such a large scale, if correct, must lead to distrust of the electrocardiogram as a diagnostic tool in this race and, in view of the current interest in the supposed freedom of the Bantu from coronary disease, would confuse the position even more.

We are unable to accept Grusin's findings and are satisfied that the electrocardiogram is a valuable diagnostic aid in Bantu heart disease. In support of this statement we produce in this paper evidence of its reliability, but before describing our results we wish to comment on Grusin's findings, which he classified into the 3 following patterns.

From Edendale Hospital, Pietermaritzburg, Natal, South Africa.

Pattern 1. Deeply inverted T waves, usually, but not always, confined to the right precordial leads with depression of J and an upwardly bowed S-T segment, the T wave ending in a hump before settling to the isoelectric line. This pattern occurred in 14 per cent of healthy nurses, 34.1 per cent of cardiac cases, and 53.9 per cent of noncardiac medical admissions.

Pattern 2. Elevation of the S-T segment and a tall bold T wave with a slowly rising ascending limb and a sharply falling distal limb ending in a U wave. These features were almost invariably confined to the left precordial leads. This pattern occurred in 4 per cent of healthy nurses, 29.3 per cent of cardiac patients, and 25.2 per cent of noncardiac patients.

Pattern 3. This covered the wide range from the loss of the normal concavity of the S-T segment with rounding of the peak of the T wave to complete flattening of this wave. No details were given as to the leads in which these changes were found. This pattern occurred in 4 per cent of healthy nurses, none of cardiac cases, and 4 per cent of noncardiac patients.

These patterns thus embrace most changes in the precordial end deflection, ranging from tall, upright T waves with elevated S-T segments, through flattening of the T wave, to inverted T waves with depressed S-T segments, or raised S-T segments. This last observation was not commented upon by Grusin but is shown in his illustrations.

Of the 250 subjects studied by Grusin, only 50 were in good health; the remainder con-

TABLE 1.—*Age Grouping of Cardiac Patients*

Ages	Rheumatic	Syphilitic	Hypertensive	Pulmonary	Congenital	Infarction	Pericarditis	Total
5—14	—	—	—	—	1	—	—	1
15—24	6	—	—	—	—	1	—	7
25—34	12	2	1	1	1	1	3	21
35—44	7	—	11	1	1	2	5	27
45—54	3	3	4	4	—	—	2	16
55—64	2	1	5	3	—	—	—	11
65+	—	4	10	3	—	—	—	17
Totals	30	10	31	12	3	4	10	100
Proved*	5	—	5	—	—	4	4	18

*Autopsy or operation.

sisted of 159 consecutive noncardiac medical admissions and 41 consecutive cardiac admissions. Abnormal electrocardiograms were almost 3 times more commonly seen in both groups of patients than in the healthy controls. It seems unwise to assume that these changes in the T wave and S-T segments can be ascribed to functional causes when so many other important factors may have been present in the patients. It would not appear unreasonable that a considerable proportion of consecutive medical admissions would be complicated by factors such as electrolyte imbalance, infections, or metabolic disorders, all of which may cause alterations in the ST-T complex.[3, 4] This would indeed appear to be the case as, of the 11 examples illustrated, no fewer than 9 patients were suffering from infections that included typhoid fever, pneumonia, acute bronchitis, and pleural effusion. In some of these, myocarditis would seem difficult to exclude.

In the group of 41 cardiac patients, it appears impossible to accept that electrocardiographic patterns resembling those found in heart disease can be ascribed to functional rather than organic causes in the absence of autopsy proof or details of the nature of the cardiac lesions known to be present.

It would seem that only in the control group could these changes properly be ascribed to functional causes, but here lack of full information on the extent of the T-wave inversions leaves doubt as to the significance of these changes. There is clearly a great difference in importance between T-wave inversion in the right precordial leads, and inversion of the T in the left precordial leads. In the case of the former, inversion of the T as far across as V_4 may be normal when accompanied by an rS, or RS, pattern.[4] Such a persistence of the juvenile pattern is found in other races, such as the American Negro, and in the Puerto Ricans,[6] and is accepted not to be organic.

Pattern 2 is admittedly similar to that found in the early stages of acute pericarditis but in the control group serial studies did not show the subsequent changes found in this disease, and differentiation could thus have been made without great difficulty.

Pattern 3 covers such a wide range of T-wave changes that the finding of only 2 instances of this variegated pattern in the control group appears scarcely to justify its inclusion as a special pattern.

As part of our larger study of heart disease in the Bantu it was necessary to clarify the value of the electrocardiogram in these people, and an investigation was carried out of the tracings in health and heart disease.

METHODS AND MATERIAL

Control Group. Fifty healthy female nurses between 21 and 38 years of age, and 50 healthy male nurses and orderlies, of ages between 19 and 36, were used as controls. In addition to physical, radiologic, and electrocardiographic examinations various blood investigations were carried out. These included estimation of the serum electrolytes, liver function tests, complete blood counts, and the Wassermann reaction.

Cardiac Group. The electrocardiograms of 100 cardiac patients were studied. No cases were included in which the clinical diagnosis appeared to be doubtful and in 18 instances postmortem or operative proof was obtained. Cases with the possibility of more than 1 etiologic factor were excluded, e.g., hypertension complicating pulmonary heart disease, and in view of the possibility of complicating ischemia from involvement of the coronary arteries or their ostia by atherosclerosis or syphilis, no case giving a history of exertional precordial pain was included. With 4 exceptions added to bring the numbers up to 100 cases, all

TABLE 2.—*Diseases Causing Hypertrophy of One or More Chambers of the Heart*

Electrocardiographic changes	Rheumatic				Syphilitic	Pulmonary	Hypertensive	Congenital
	M.S.	M.I.	A.I. or M.I.	A.I.	A.I.			
Normal	4	0	2	1	2	4	4	0
> 0.11 sec.	6		1					
> 2.5 mm. tall						1		1
Partial heart block	3		2					
Atrial fibrillation	3		1					
Right ventricular hypertrophy	7		1	1		3		2
Delayed right ventricular conduction	3					1		1
Right bundle-branch block						1	1	
Left ventricular hypertrophy			4		3		11	
Incomplete left ventricular hypertrophy			1		1		9	
Left bundle-branch block					1		3	
Flat TS in left precordial leads	3				1	2		
High voltage							4	
Diminishing R across chest	1	1			1			
Grusin's pattern 2	1							
Totals	16	1	12	2	9	12	31	3

M.S. = Mitral stenosis. M.I. = Mitral incompetence. A.I. = Aortic incompetence.

these patients were admitted during a period of 6 consecutive months. Eighty-five per cent of these patients came from the rural areas served by this hospital, the remainder being from the urban areas in and around the city of Pietermaritzburg.

We have used in this paper the accepted normal standards as laid down by Goldberger[4] and Myers,[7] but it is realized that in the measurements of the minute fractions of time and distance a certain amount of "observer error" must creep in, particularly in estimation of the duration of the QRS and Q-T intervals.

RESULTS

Control Group

On the whole, the tracings were normal by accepted standards; the 5 per cent showing deviations are discussed below. Excepting sinus arrhythmia no abnormalities of rhythm were found. The duration of the QRS tended to be short, ranging from 0.04 to 0.08 second with an average in both sexes of 0.06 second. The Q-T interval averaged in males 39.7 seconds and in females 38.8 seconds, figures not unlike those obtained in other races.

Abnormalities in Control Group. Partial heart block was seen in 1 male, the P-R interval being 0.28 second. It seems probable that some undiagnosed pathology was present, but he left our service before further investigations could be carried out.

The precordial T wave was inverted as far across as V_3 in 1 female. In an additional female and in 1 male, the T wave was inverted in leads V_1 and V_2. An rS or RS pattern accompanied all these T-wave inversions. The electrocardiograms were repeated at a later date and leads were taken in addition to the V leads. It was found that all the leads showed upright T waves with the exception of 1 in the female who showed inversion of the T wave as far across as V_3.

Grusin's pattern 2 was seen in 2 males in leads V_4 and V_5 only; the pattern persisted unchanged for more than 6 months.

Cardiac Group

The causes of the heart diseases under study have been given in table 1. Table 2 shows the electrocardiographic changes found in diseases where the lesions caused hypertrophy of 1 or more chambers of the heart, while table 3 gives the findings in cases where the heart muscle was damaged either by ischemia or by infarction.

Changes due to Hypertrophy. With the few exceptions mentioned below, the findings

TABLE 3.—*Electrocardiographic Abnormalities of Damage to Heart Muscle by Ischemia or Infarction*

	Peri-carditis	Myo-cardial infarct	Total abnor-malities
Normal	0	0	0
Low voltage	5	0	5
Depression of S-T segments	4	0	0
Elevation of S-T segments	0	1	0
Inverted precordial T waves	7	1	8
Flat precordial T waves	2	0	2
Biphasic precordial T waves	1	0	1
Abnormal Q waves	0	1	1
Left bundle-branch block	0	2	2
Diminishing R across precordium	0	1	1
Total cases	10	4	14

in table 2 resemble closely those that would be expected in similar circumstances in any other race.

1. Right ventricular hypertrophy associated with aortic incompetence. This may have been due to failure to detect an additional mitral stenosis, as this tracing was obtained from a female aged 36 years in whom a rheumatic etiology was suspected.

2. Diminishing R waves across the chest. This occurred in the following: (a) A man aged 26 who suffered repeated attacks of congestive failure following mitral valvotomy. Embolism of a coronary artery seemed the likely cause (fig. 1). (b) A woman aged 27 who had sustained a syphilitic cerebral thrombosis, and later developed aortic incompetence. (c) A woman aged 20 with a huge heart caused by mitral incompetence. Microscopy showed only hypertrophy of the muscle fibers. While the r wave failed to increase, no Q wave was present.

3. Grusin's pattern 2 occurred in 1 male suffering from mitral stenosis. Serial changes revealed no change suggestive of pericarditis.

Changes due to Myocardial Damage. Pericarditis. Pericardial effusion, thought to be tuberculous, was found in 7 cases. Occlusive pericarditis, proved to be tuberculous, was present in the other 3 cases.

Myocardial Infarction. The youngest patient was aged 22 years. He had an anterior infarct near the interventricular septum, and the electrocardiogram showed left bundle-branch block without an abnormal Q wave.

Diminishing R wave across the chest. This feature was found in a man aged 44 who was admitted in acute cardiac failure with no history of precordial pain. During a very stormy illness lasting 2 months electrocardiogram showed transient elevations of the S-T segment and persistent diminution of the R wave across the precordium as far as between V_4 and V_5, where a small localized Q wave was found. V_5 showed an RS pattern, the qR pattern not starting until V_6. He recovered but was readmitted 4 months later and died before a history or an electrocardiogram could be obtained. Autopsy revealed an old posterolateral infarct affecting the epicardial two thirds of the muscle and several areas of fibrosis about the size of a matchhead in the anterior wall of the left ventricle. At no time did lead aV_F show changes suggestive of infarction (fig. 2).

The other 2 infarcts occurred in men aged 31 and 44 years respectively. In one case a large infarct near the apex was associated with a left bundle-branch block; in the other a large anterior infarct of the left ventricle was associated with classical electrocardiographic changes.

DISCUSSION

From our study of the electrocardiogram of the healthy, normal Bantu it appears that, with few exceptions, the patterns do not differ to any significant extent from those in other races. We agree with Grusin that in health the patterns he described are probably due to functional causes and are of no significance.

In our admittedly small series of 100 cases of cardiac disease few differences from the disease pattern in other races were found, and these, it would seem, could be accounted for by misdiagnosis rather than by any racial trait, the error lying more likely with the observer than with the electrocardiogram.

Certain observations may be made on the low incidence of Grusin's patterns among the group of cardiac cases. It is not uncommon to find, among the Bantu, cases of "failed hyper

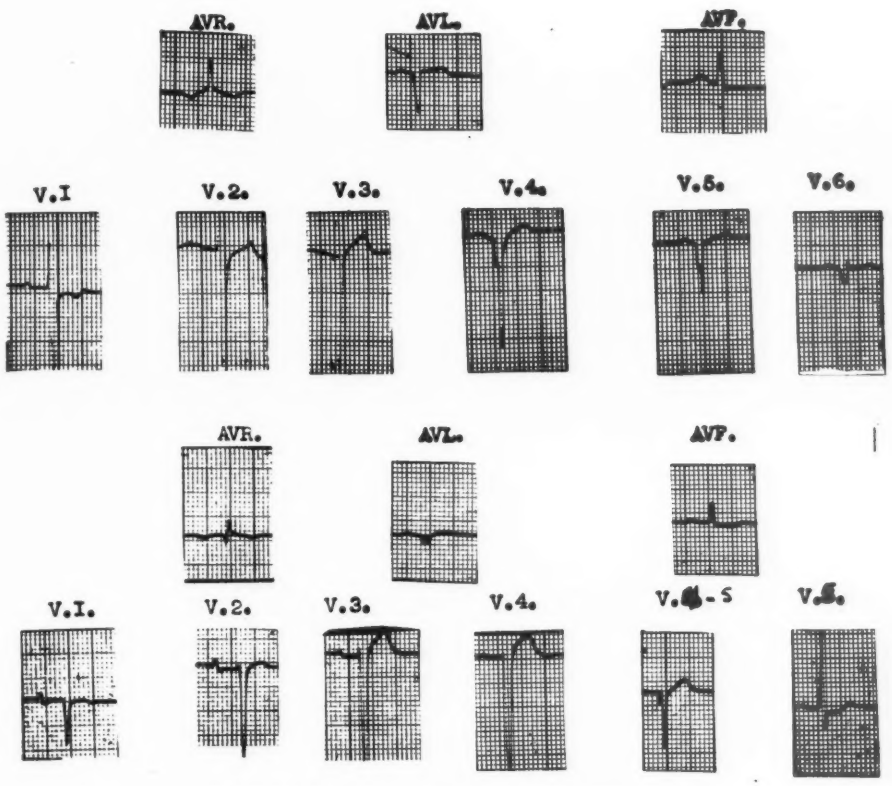


FIG. 1 *Top.* Diminishing R waves across the precordium.
FIG. 2 *Bottom.* Diminishing R waves from V_1 to V_4.

tension," i.e., cardiac patients with normal blood pressures in whom previous histories reveal that they had previously been treated for hypertensive cardiac failure. Also, in the postmortem room we commonly come upon normotensive cases of cardiac failure in whom there is evidence of left ventricular hypertrophy associated with renal changes compatible with the presence of hypertension. In the series of 31 cases of hypertensive cardiac failure presented in this paper, 4 cases, now normotensive, were found from previous records to have had hypertension in the past. In all of these the electrocardiogram showed left ventricular hypertrophy. This phenomenon is known to occur in other races, but frequently the diastolic pressure remains above the limits of normal.[8] In the Bantu the fall is often greater and to well within the accepted limits of normal; in the absence of previous records diagnosis becomes difficult. It is conceivable that this factor may have influenced some of Grusin's tracings.

CONCLUSIONS

It would appear that there is no reason for the assumption that the electrocardiogram of the South African Bantu differs in any important respect from that obtained in other races. It would follow that when patterns suggesting specific types of heart disease are found, they must be given the same consideration as would be given were the changes found in individuals of other races.

Summary

The electrocardiograms of 100 healthy Bantu adults of both sexes and the electrocardiograms of 100 Bantu suffering from heart disease have been studied. It is concluded that neither in health nor in disease do the electrocardiograms differ significantly from those obtained in similar circumstances from other racial groups.

Acknowledgment

We wish to thank the Director of Hospital Services for Natal, Dr. J. L. Parker, and the Superintendent of Edendale Hospital, Dr. T. M. Adnams, for permission to publish this paper. We also wish to thank the Matron and Nursing Staff of this hospital for their cooperation in providing the control group of subjects.

Summario in Interlingua

Esseva studiate le electrocardiogrammas de 100 normal bantus adulte de ambe sexos e de 100 bantus con morbos cardiac. Le conclusion es que le electrocardiogramma del bantu —tanto in stato de bon sanitate como etiam sub conditiones pathologic—non differe significativemente ab le electrocardiogramma de altere gruppos racial sub simile circumstantias.

REFERENCES

1. Mann, G. V.: The epidemiology of coronary heart disease. Am. J. Med. **23:** 463, 1957.
2. Grusin, H.: Peculiarities of the African's electrocardiogram and the changes observed in serial studies. Circulation **9:** 860, 1954.
3. White, P. D.: Heart Disease. New York, The Macmillan Company, 1951.
4. Goldberger, E.: Unipolar Lead Electrocardiography and Vectorcardiography. Philadelphia, Lea & Febiger, 1953.
5. Littmann, D.: Persistence of the juvenile pattern in the precordial leads of healthy adult Negroes, with report of electrocardiographic survey on 300 Negroes and 200 white subjects. Am. Heart J. **32:** 370, 1946.
6. Suarez, A. M., and Suarez, R. M.: The T wave of the precordial electrocardiogram at different age levels. Am. Heart J. **32:** 480, 1946.
7. Myers, G. B.: The Interpretation of the Unipolar Electrocardiogram. St. Louis, C. V. Mosby Company, 1956.
8. Fishberg, A. M.: Hypertension and Nephritis. Philadelphia, Lea & Febiger, 1955.

Frandsen, E.: Visual Manifestations of Digitalis Poisoning. Two Cases of Toxic Amblyopia. Acta. med. scandinav. **157:** 51 (March 10), 1957.

Two patients were observed to develop central scotomata while receiving digitalis. The first patient, a 67-year-old woman, had received 6 tablets daily of digitalis leaf for 1 week when visual deterioration to 6/60 bilaterally and some nausea were noted. Moderate improvement in vision occurred after stopping the daily maintenance dose of 1 digitalis tablet 5 months later. The second patient, a 60-year-old man, developed visual weakness to 6/9 (O.D.), 6/12 (O.S.) with fluttering colored hallucinations, vomiting, and bigeminy after taking Digitalan for 3 or 4 years in unknown quantities. Considerable improvement in these symptoms occurred on stopping the drug and administering potassium iodide plus vitamin B. The various toxic effects of digitalis therapy are described.

Rogers

Determinants of the Left Atrial Pressure Pulse in Mitral Valve Disease

By NEIL A. J. HAMER, M.B., M.R.C.P., SUJOY B. ROY, M.B., M.R.C.P., AND JAMES W. DOW, M.D.

The difficulties of preoperative evaluation of patients with combinations of mitral stenosis and incompetence prompted analysis of the left atrial pressure pulse in a series of patients studied by left atrial puncture. Theoretic considerations indicate that similar pressure pulses may be produced by a variety of mitral valve lesions if the volume-pressure characteristics of the left atrium are appropriate. An explanation is offered for the differences found in the presence of mitral regurgitation.

UNCOMPLICATED mitral stenosis and mitral incompetence are easily distinguished clinically and produce characteristic changes in the left atrial pressure pulse. Patients with a combination of stenosis and incompetence are more difficult to evaluate. The mitral diastolic pressure gradient and the cardiac output can be obtained by current techniques, but for complete assessment in the presence of mitral incompetence an estimate of regurgitant flow is necessary. This has been attempted by indicator-dilution methods,[1-4] rapid biplane angiocardiography,[5] and ultrasonic echo technics.[6] None of these approaches is free from practical or theoretic objection.

Several attempts have been made to evaluate mitral valve disease from the left atrial pressure pulse, or from the similar pressure pulse obtained when a catheter is wedged in a peripheral pulmonary artery. Methods based on the height of the v wave[7-10] have been found less useful than indices derived from the y descent.[11, 12] Several workers have concluded that the left atrial pressure pulse is of little value in establishing the presence of mitral incompetence.[13-17] To clarify the factors responsible for variations in the left atrial pressure pulse, a small series of patients with mitral valve disease has been reviewed.

From the Tufts Medical Services and Circulation Laboratory, Boston City Hospital and the Department of Medicine, Tufts University School of Medicine.

Supported by Grant No. HT5012-C5 from the National Heart Institute.

METHODS

Patients with mitral stenosis were studied when clinical evaluation was difficult because of associated mitral incompetence, aortic valve disease (5 cases), previous valvotomy (1 case), or doubt as to the severity of the lesion. Estimates of the size of the mitral valve orifice and the regurgitant flow were obtained at operation in all subjects. In 4 cases autopsy details were also available. Adequate data were available in 15 patients (table 1).

Left atrial puncture was made by the posterior route as described previously.[18] Left ventricular pressures were recorded in all but 4 cases. Right heart catheterization was carried out to determine the cardiac output. Pressures were recorded with Statham P23Db strain-gage manometers, with use of Sanborn direct-writing equipment at a paper speed of 50 mm. per second. The base line for all pressure measurements was the middle of the chest at the level of the second costal cartilage with the patient recumbent.[19] Measurements were made in records selected for adequate frequency response. In atrial fibrillation 10 cardiac cycles were measured and in sinus rhythm 5 were measured, and the mean value was taken. The Ry/v ratio was calculated with pressures adjusted to a base line at the level of the sternal angle as used by Owen and Wood.[11]

Phasic gradients were obtained by replotting pressures at 0.05 second intervals on the same scale, the electrocardiogram being used as a control when simultaneous records were not available. The mitral valve area equivalent was calculated with use of the standard orifice formula.[20] In patients with no left ventricular pressure record a mean diastolic pressure of 5 mm. Hg was assumed. Left atrial enlargement was estimated from standard radiographs and fluoroscopy, and was graded from 1 to 4.

TABLE 1.—*Hemodynamic Data and Valve Areas in Fifteen Patients with Mitral Stenosis and Incompetence*

Patient	Sex	Age	Rhythm	Cardiac index (L./M.²/min.)	Mean mitral diastolic gradient (mm. Hg)	Calculated mitral valve area (cm.²)	Operation findings: Valve area (cm.²)	Operation findings: Regurgitation (0 to 4)	Left atrial size (1 to 4)
Mitral stenosis									
P.C.	M	43	AF	2.2	19	0.8	1.0	1	3
T.E.	M	42	AF	2.4	21	0.8	0.8	1	1
D.H.	F	28	NS	2.8	5	1.0	0.8	0	1
L.H.	F	39	AF	2.5	13	1.0	0.8	1	4
S.H.	F	39	NS	3.1	21	1.2	1.2	0	2
W.H.	F	54	AF	1.6	5	1.0	0.8	1	2
E.O.	F	17	NS	3.2	27	0.8	1.0	0	2
J.Q.	M	23	NS	3.0	16	0.8	1.0	1	1
H.R.	F	51	AF	1.5	7	0.9	0.8	1	2
M.S.	F	61	AF	1.2	16	0.4	0.4	1	3
Mean		40		2.4	14	0.8	0.9	0.7	2.2
Mitral incompetence									
E.D.	F	53	AF	2.7	7	1.7	2.0	3	3
M.G.	F	33	AF	2.6	4	1.8	2.5	3	4
D.L.	M	36	NS	1.6	13	0.6	1.2	2	3
E.M.	F	29	NS	3.0	15	1.3	3.0	3	3
J.P.	F	48	AF	1.4	12	0.6	3.0	3	3
Mean		40		2.5	10	1.2	2.4	2.8	3.2

Hypothetical diagrams of phasic flow changes were constructed from a series of characteristic pressure curves with a cycle length of 0.6 second, a diastolic filling time of 0.33 second, and a mean mitral diastolic gradient of 16 mm. Hg. A stroke volume index of 30 ml. was assumed, giving a mitral valve area index of 0.7 cm.²

RESULTS

The 15 patients were divided into 2 groups. In 10 patients mitral incompetence was either absent or insignificant. The remaining 5 patients had considerable narrowing of the mitral valve, but gross regurgitant jets were felt by the surgeon. The incidence of atrial fibrillation was similar in each group, but the left atrium tended to be larger in patients with mitral incompetence. The observed and calculated mitral valve areas were similar in the stenotic group (table 1).

The y descent of the left atrial pressure pulse was analyzed by 3 methods. When the rate of the y descent was related to the height of the v wave (Ry/v),[11] there was no clear-cut separation of the stenotic and incompetent groups, though a trend to higher values was evident in the presence of regurgitation. Similar results were obtained when the mean left atrial pressure was taken as a reference level (Ry/LAP).[12] Use of the first 0.1 second of the y descent ($Ry^{0.1}$/LAP)[12] showed some advantage in that 2 patients (E.D. and M.G.) in the incompetent group were clearly distinguished (fig. 1). These were the only patients in which the left atrial and ventricu

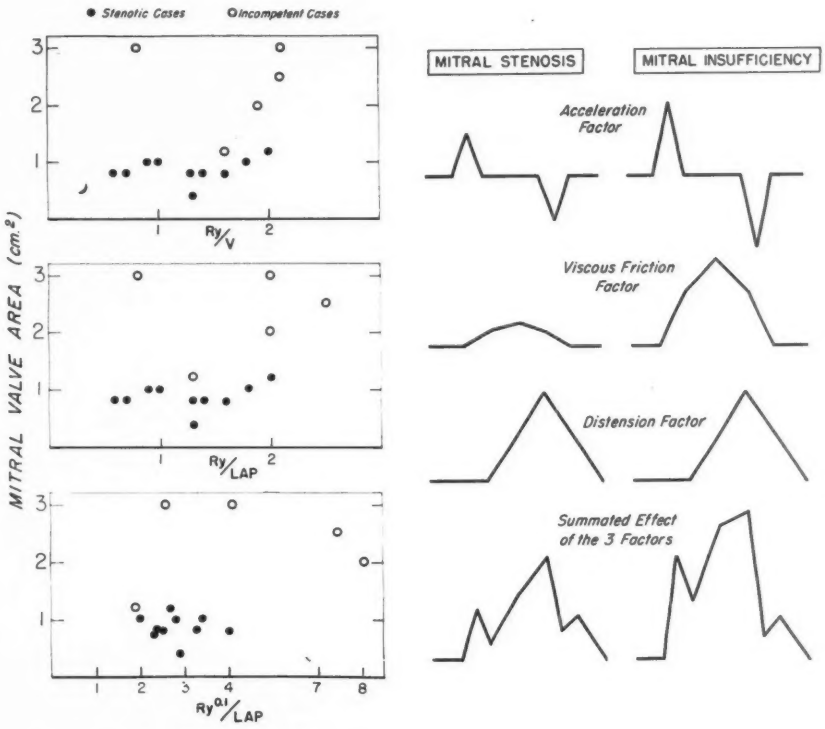


FIG. 1 *Left.* Ratio of rate of the y descent to level of left atrial pressure by 3 different methods in 15 patients with mitral valve disease.

FIG. 2 *Right.* Diagrammatic representation of left atrial pressure pulse in mitral valve disease. Modification of Peterson's analysis[21] of pressure response to injection of a test volume into an isolated segment of the vascular system. The summated effect of the 3 factors resembles the left atrial pressure pulse in mitral disease with atrial fibrillation. Viscous friction is shown to vary with rate of flow into left atrium. Larger acceleration and viscous friction components may be responsible for a distinctive pressure pulse when mitral stenosis is complicated by insufficiency.

l r pressures became identical at the end of d iastole.

Discussion

The Mechanism Producing Pressure Changes in the Left Atrium. Peterson[21] stud- i d the parameters determining the pressure 1 sponse to pulsatile blood flow in large ar- t ries and veins. He concluded that 3 factors ere involved: acceleration, viscous friction, ıd distensibility. The introduction of a test olume into an isolated segment of the vascu- r system produces a brief pressure transient ue to the acceleration factor and the devel- oment of viscous friction. Sustained flow is associated with a constant pressure due to viscous friction. If distention occurs, there is an additional pressure rise related to the physical characteristics of the system. These factors are illustrated in figure 2.

The similarity of the patterns derived from Peterson's study[21] and the left atrial pressure pulse in patients with mitral valve disease and atrial fibrillation (fig. 3) suggested the application of these considerations to the analysis of the left atrial pressure pulse.

In mitral valve disease distention of the left atrium is a continuing factor, and the distensibility of the left atrial wall is a major

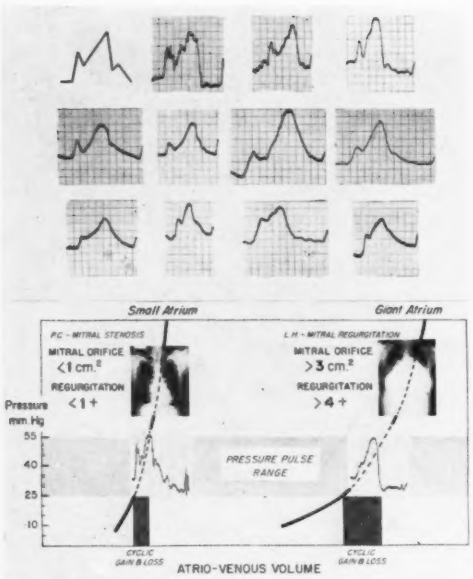


FIG. 3 *Top.* Left atrial pressure pulse in 11 patients with mitral valve disease. Comparison of the theoretical diagram, after Peterson,[21] and the left atrial pressure pulse in 11 patients with mitral valve disease and atrial fibrillation.

FIG. 4 *Bottom.* Atrial pressure pulse expressed as travel along atriovenous volume pressure curve. Left atrial volume-pressure curve in 2 patients, one with mitral stenosis and a small atrium, the other with mitral regurgitation and a giant atrium. Cyclic volume gain and loss is greater in patient with regurgitation, but range of pressure change is similar to the stenotic case as the volume-pressure curve rises less steeply.

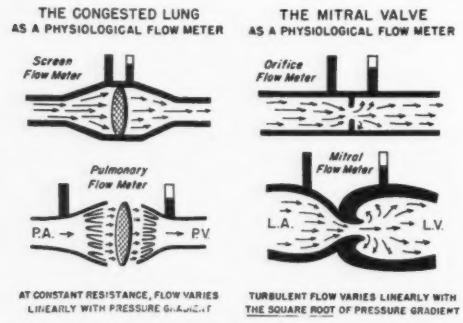


FIG. 5. Pulmonary vascular bed may be regarded as a screen flowmeter, flow varying linearly with pressure gradient. The mitral valve acts as an orifice flowmeter, flow varying with square root of gradient. Phasic flow changes may be estimated from variations in gradient.

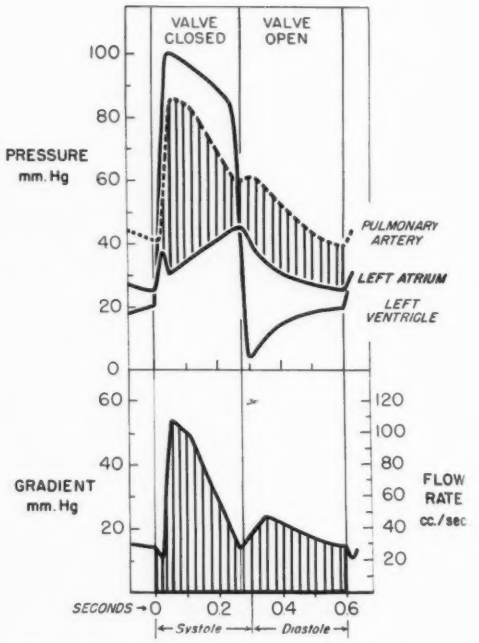
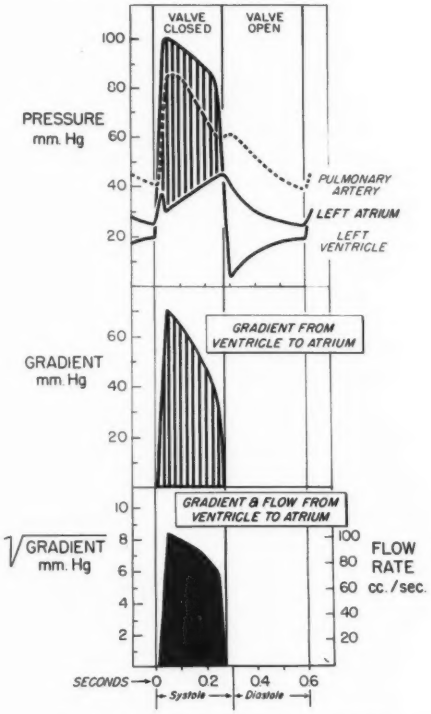


FIG. 6. Phasic pressure gradient and flow rate across pulmonary vascular bed in hypothetical example of mitral valve disease with atrial fibrillation. Assuming a stroke volume index of 30 ml., the mean flow rate is 50 ml./sec. Flow is linearly related to pressure gradient and is maximal in early systole.

determinant of the pressure pulse. The relation of volume to pressure is not constant, but pressure changes are greater for a given volume change as the pressure rises. This is expressed as the volume-pressure curve (fig. 4), and variations in pressure with cyclic changes in volume may be regarded as movement along this curve.

Additional pulses are superimposed on this basic pattern. These include acceleration transients and viscous friction effects as described by Peterson,[21] and changes due to atrial systole and diastole. The subsequent discussion is confined to the passive fibrillating atrium.

The Left Atrial Pressure Pulse as Movement Along a Volume-Pressure Curve. The mitral valve and the pulmonary vascular bed may be regarded as physiologic flowmeters of the orifice and the screen types (fig. 5). Phasic



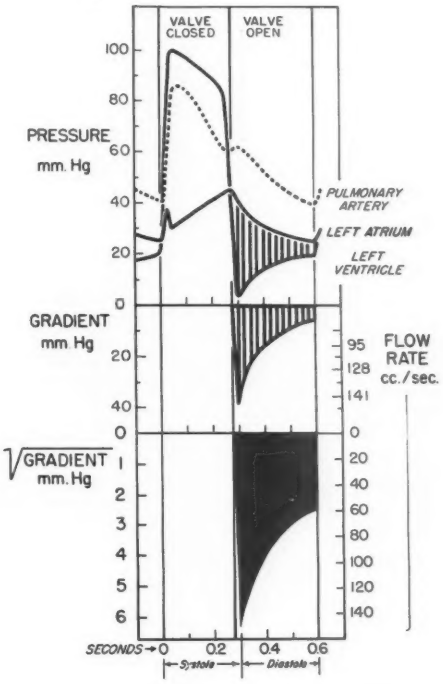


FIG. 7 *Left.* Phasic pressure gradient and flow across incompetent mitral valve in systole in hypothetical example. Assuming a regurgitant flow index of 25 ml. per beat, the mean flow rate is 82 ml./sec. Flow is proportional to square root of gradient and is maximal in early systole.

FIG. 8 *Right.* Phasic pressure gradient and flow rate across stenotic mitral valve in diastole in hypothetical example. Assuming a stroke volume index of 30 ml., the mean flow rate is 90 ml./sec. Flow is proportional to square root of gradient and is maximal immediately after valve opens.

changes in the pressure gradients are related to the variations in flow. At the mitral orifice, flow is turbulent and varies with the square root of the gradient. There is good evidence that the congested pulmonary vasculature behaves as a constant resistance,[22] and flow across the lungs is therefore related directly to the pressure gradient. The significance of the phase difference between flow and pressure[23] is difficult to evaluate and will not be considered here.

Hypothetic diagrams have been constructed to show the relationship between pressure gradient and flow across the pulmonary vascular bed (fig. 6) and through the mitral orifice in systole (fig. 7) and diastole (fig. 8) in mitral valve disease with atrial fibrillation. Flow into the left atrium from the lungs and through an incompetent mitral valve have similar time relations, reaching a peak in early systole and being curtailed in late systole by the rise in left atrial pressure. As rapid filling occurs on the lower, flatter part of the volume-pressure curve, a steady rise in left atrial pressure throughout systole results. When mitral incompetence complicates mitral stenosis, the magnitude but not the timing of the volume changes is affected (fig. 9).

The viscoelastic properties of the left atrium are important determinants of the pressure pulse.[7, 8, 11, 24, 25] The absence of any correlation between left atrial volume and

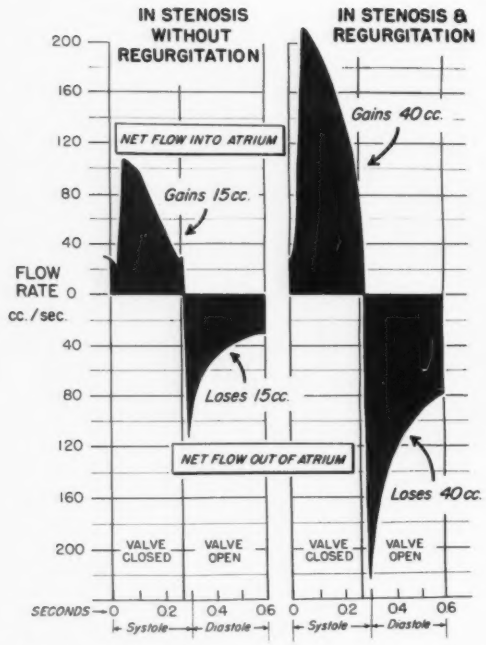


FIG. 9. Summated effects of phasic flow into and out of fibrillating left atrium in mitral stenosis and in stenosis with regurgitation. The same values for stroke volume index (30 ml.) and regurgitant flow (25 ml.) are used as in the previous figures. Half the pulmonary venous flow (15 ml.) occurs when mitral valve is closed. During systole, flow into left atrium from lungs and flow through incompetent mitral valve have similar time relations. Therefore when regurgitation complicates mitral stenosis, only the magnitude of phasic volume changes is affected. Both situations are compatible with the same series of pressure curves if physical properties of left atrium are appropriate, the calculated mitral valve area index being 0.7 cm.^{2} in isolated stenosis and 1.3 cm.^{2} when a combination of stenosis and incompetence is assumed.

pressure[26-29] is evidence that the physical properties of the chamber vary from case to case. As the phasic volume change does not differ in timing in mitral stenosis and in combined stenosis and incompetence, a more distensible left atrium in the presence of regurgitation would result in a similar pressure pulse in the 2 situations. The tendency of the left atrium to be larger in mitral incompetence has a similar effect.

When the left atrial pressure pulse is considered as movement along a volume-pressure curve, it is apparent that a similar appearance is to be expected in pure mitral stenosis and in mitral stenosis with incompetence.

Acceleration Transients and Viscous Friction Effects. Acceleration transients are evident when there is a sudden change in the direction of blood flow. At the onset of ventricular systole the c wave appears to interrupt the steady rise in left atrial pressure. It probably represents an acceleration transient due to the abrupt check or reversal of flow through the mitral valve. At the peak of the v wave, the rapid outflow from the atrium when the mitral valve opens is associated with a corresponding negative effect that accentuates the initial phase of the y descent, and may produce a notch between this phase and the later, more gradual fall in left atrial pressure. In the presence of mitral incompetence the volume changes are greater, and these effects are accentuated (fig. 2).

Viscous friction produces a rise in pressure that is related to the velocity of flow.[21] The velocity of systolic flow into the left atrium is greater in mitral incompetence than in isolated mitral stenosis. The viscous friction effect is therefore larger and will tend to make the ascending limb of the v wave more prominent (fig. 2).

The factors described will cause the left atrial pressure pulse to deviate from the pattern predicted on the basis of the volume-pressure curve. The increased prominence of these effects in the presence of mitral regurgitation is probably responsible for the partial success of the Ry/v ratio[11] and similar indices in distinguishing these patients.

SUMMARY

The left atrial pressure pulse in atrial fibrillation is an expression of travel along a volume-pressure curve during cyclic volume gain and loss.

Pressure changes due to acceleration transients and viscous friction effects are superimposed on this basic pattern.

An infinite number of combinations of ste-osis and insufficiency could account for any ressure pulse, assuming larger, more disten-ble atria with increasing regurgitation.

No estimate of relative stenosis and insuf-iciency can be expected from the form of the ressure pulse in any individual case without nowledge of the atrial volume-pressure curve.

Larger acceleration transients and viscous iction effects may account for partial suc-ss of the Ry/v ratio and other methods in istinguishing mitral incompetence in the resence of stenosis.

Summario in Interlingua

Le pulso de pression sinistro-atrial in fibril-lation atrial es un expression de movimento sequente le curva de volumine e pression in le curso de un cyclo de ganio e perdita de volu-mine.

Alterationes del pression resultante de tran-sientes de acceleration e de effectos de friction viscose es superimponite a iste configuration fundamental.

Un numero infinite de combinationes de stenosis e insufficientia esserea capace a expli-car omne pulso de pression. In isto nos sup-pone que plus grande e plus distensibile atrios occurre con augmentos del regurgitation.

Nulle estimation del relative stenosis e in-sufficientia pote esser basate super le forma del pulso de pression in le caso individual in le absentia de informationes concernente le curva de volumine e pression atrial.

Plus grande transientes de acceleration e effectos de friction viscose explica possibile-mente le successo partial effectuate per le methodo a proportion de Ry/v e altere metho-dos i nestablir le distinction de incompetentia mitral in le presentia de stenosis.

REFERENCES

1. Korner, P. I., and Shillingford, J. P.: The quantitative estimation of valvular incompetence by dye dilution curves. Clin. Sc. **14**: 533, 1955.
2. Shillingford, J.: Simple method for estimating mitral regurgitation by dye dilution curves. Brit. Heart J. **20**: 229, 1958.
3. Keys, J. R., Swan, H. J. C., and Wood, E. H.: Dye-dilution curves from systemic arteries and left atrium of patients with valvular heart disease. Proc. Staff Meet., Mayo Clin. **31**: 138, 1956.
4. Haynes, F., Novack, P., Schlant, R., Phinney, A., and Dexter, L.: Hemodynamics of mitral stenosis and regurgitation. Fed. Proc. **16**: 56, 1957.
5. Smith, P. W., Cregg, H. A., and Klassen, K. P.: The diagnosis of mitral regurgitation by cardioangiography. Circulation **12**: 777, 1955.
6. Effert, S., Erkens, H., and Grosse-Brockhoff, F.: The ultrasonic echo method in cardiological diagnosis. German M. Month. **2**: 325, 1957.
7. Allison, P. R., and Linden, R. J.: Bronchoscopic approach for measuring pressure in left auricle, pulmonary artery, and aorta. Lancet **1**: 9, 1955.
8. Connolly, D. C., Burchell, H. B., Kirklin, J. W., and Wood, E. H.: Pulmonary-artery wedge pressure in relation to detection of mitral insufficiency. Fed. Proc. **14**: 30, 1955.
9. Fox, I. J., Wakai, C. S., Connolly, D. C., and Wood, E. H.: Left atrial and ventricular pressure pulses in mitral valvular disease. Proc. Staff Meet., Mayo Clin. **31**: 126, 1956.
10. Kent, E. M., Ford, W. B., Fisher, D. L., and Childs, T. B.: The estimation of the severity of mitral regurgitation. Ann. Surg. **141**: 47, 1955.
11. Owen, S. G., and Wood, P.: A new method of determining the degree or absence of mitral obstruction: An analysis of the diastolic part of indirect left atrial pressure tracings. Brit. Heart J. **17**: 41, 1955.
12. Morrow, A. G., Braunwald, E., Haller, J. A., and Sharp, E. H.: Left atrial pressure pulse in mitral valve disease: A correlation of pressures obtained by transbronchial puncture with the valvular lesion. Circulation **16**: 399, 1957.
13. Wynn, A., Matthews, M. B., McMillan, I. K. R., and Daley, R.: The left auricular pressure pulse in normals and in mitral valve disease. Lancet **2**: 216, 1952.
14. Venner, A., and Holling, H. E.: Comparison of operation and clinical findings in mitral stenosis and incompetence. Brit. Heart J. **15**: 205, 1953.
15. Goodwin, J. F., Hunter, J. D., Cleland, W. P., Davies, L. G., and Steiner, R. E.: Mitral valve disease and mitral valvotomy. Brit. M. J. **2**: 573, 1955.
16. Ankeney, J. L., Fishman, A. P., and Fritts, H. W.: An analysis of normal and abnormal

left atrial pressure pulses in man. Circulation Research **4**: 95, 1956.

17. Gordon, A. J., Kuhn, L., Amram, S. S., Donoso, E., and Braunwald, E.: Left atrial "pulmonary capillary," and esophageal balloon pressure tracings in mitral valve disease. Brit. Heart J. **18**: 327, 1956.
18. Gadboys, H. L., Roy, S. B., and Dow, J. W.: Simplified procedure for combined heart study. Ann. Surg. **146**: 843, 1957.
19. Roy, S. B., Gadboys, H. L., and Dow, J. W.: Base line for left heart catheterization. Am. Heart J. **54**: 753, 1957.
20. Gorlin, R., and Gorlin, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. I. Am. Heart J. **41**: 1, 1951.
21. Peterson, L. H.: The dynamics of pulsatile blood flow. Circulation Research **2**: 127, 1954.
22. Borst, H. G., McGregor, M., Wittenberger, J. L., and Berglund, E.: Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. Circulation Research **4**: 393, 1956.
23. Burger, H. C., Van Brummelen, A. G. W., and Dannenburg, F. J.: Theory and experiments on schematized models of stenosis. Circulation Research **4**: 425, 1956.
24. Gorlin, R., Lewis, B. M., Haynes, F. W., Spiegl, R. J., and Dexter, L.: Factors regulating pulmonary "capillary" pressure in mitral stenosis. Am. Heart J. **41**: 834, 1951.
25. Fisher, D. L.: The use of pressure recordings obtained at transthoracic left heart catheterization in the diagnosis of valvular heart disease. J. Thoracic Surg. **30**: 379, 1955.
26. Gorlin, R., Houssay, H. E. J., Haynes, F. W., and Dexter, L.: Clinical and physiological correlations in patients with mitral stenosis. Am. Heart J. **43**: 2, 1952.
27. Wade, G., Werko, L., Eliasch, H., Gidlund, A., and Lagerlof, H.: The hemodynamic basis of the symptoms and signs in mitral valvular disease. Quart. J. Med., n.s., **21**: 361, 1952.
28. Wood, P.: An appreciation of mitral stenosis. Brit. M. J. **1**: 1051, 1113, 1954.
29. Soloff, L. A., Zatuchini, J., and Mark, G. E.: Relationship of left atrial volume to pulmonary artery and wedge pressures in mitral stenosis. Circulation **15**: 430, 1957.

Thompson, M. C., Patrick, R. T., and Wood, E. H.: Effects of Cyclopropane Anesthesia on the Circulation of Human Beings. J.A.M.A. **164**: 389 (May 25), 1957.

Seven persons without evident heart disease who were having a cholecystectomy were studied during various electroencephalographic levels of cyclopropane anesthesia. Cardiac index (by the Evans blue dilution method) and pulse rate decreased as the anesthesia deepened. Concomitantly, peripheral arterial resistance, radial arterial pressure, and superior vena caval pressure increased. Stroke volume decreased only during deep anesthesia and the central blood volume did not change significantly. These hemodynamic changes were considered possibly to be due to myocardial depression by cyclopropane or to an associated increase in circulating epenephrine-like substances; and, as the anesthesia was lightened, the circulatory alterations returned rapidly toward control levels.

Rogers

Serum Parameters as Discriminators between Normal and Coronary Groups

By Bernard S. Schlessinger, Ph.D., Fredrick H. Wilson, Jr., B.S., Lawrence J. Milch, Ph.D., and the Cardiovascular Research Group

Evaluation was undertaken of several measurements in discriminating between a group of clinically normal persons and a group of persons with definite atherosclerosis manifested by clinical myocardial infarctions. Various S_f lipoprotein classes, the serum cholesterol, the beta lipoprotein cholesterol, the lipid phosphorus, and the "atherogenic index" were included in the study. The results are presented and their significance is discussed.

IN THE past 10 years, several biochemical and biophysical tests have been suggested as possible indicators of atherosclerosis and predictors of clinical complications of this disease.[1-6] In 1950, the National Advisory Heart Council initiated a cooperative study involving 4 laboratories to evaluate 2 of these measurements as predictors of clinical complications of atherosclerosis. Serum cholesterol and lipoprotein measurements in a population (15,000) of clinically healthy men aged 40 to 59 were made among the laboratories, and the data were analyzed after a sufficient number of cases of coronary disease had occurred.

The results of the cooperative study were published in 1956.[7] During the 6 year period, the Donner Laboratory had changed the methods of serum lipoprotein measurements to include additional lipoprotein classes[8] and to correct for the effects of concentration on flotation rates.[8] These changes, as well as a dispute over the definition of "new clinical events," resulted in a division of opinion as to definitive results.[7] The Donner group claimed that the measurement of serum lipoproteins (with the refinements added in 1952) was a superior predictor of clinical complications of atherosclerosis, while the Cleveland, Harvard, and Pittsburgh groups stated that the cholesterol measurement was "at least as useful" as the lipoprotein determination.

This paper reports a preliminary study designed to evaluate the effectiveness of several serum measurements in discriminating between a group of clinically normal persons and one of persons with manifest atherosclerosis (clinical myocardial infarctions).

Methods

For this study, blood sera from a group of 24 male patients with myocardial infarction (MI) at Brooke Army Hospital, Fort Sam Houston, Texas, were utilized. The age distribution of this diseased group was determined and used as the criterion for selecting a comparable group of presumably normal individuals. This latter group (N) consisted of the 59 men between the ages of 30 and 66 taken from the total of 207 on whom satisfactory samples were received for routine analysis during the period from September 1, 1957 to January 15, 1958, and whose histories failed to indicate disease. Of the 59 normal men, 26 were persons in Pentagon executive positions, and 33 were members of the professional staff at the School of Aviation Medicine, USAF. The average age of the N group was 45 compared to an average age of 46 for the total (N + MI) population.

Each serum sample was analyzed ultracentrifugally for the concentration of S_f^o 0-12, S_f^o 12-20, and S_f^o 20-400 lipoprotein classes by methods described elsewhere.[9-11] The standard Gofman atherogenic index was calculated for each sample. Cholesterol was measured by a modification of the Bloor method[12] and lipid phosphorus by a modified Fiske-Subbarow technic.[12]

The β-cholesterol concentration was determined by a total cholesterol measurement on the top fraction of serum isolated after 15 hours of centrifugation at 79,000 $\times$ g at a medium density of 1.063 Gm./ml. Previous measurements of this

From the Department of Pharmacology and Biochemistry, School of Aviation Medicine, USAF, Randolph Air Force Base, Texas.

Members of the Cardiovascular Research Group are Harrie B. Haven, B.S., A/1C Ellis R. Pugh, and M/Sgt Bernard D. Knuth.

TABLE 1.—*Serum Parameter Efficiency for Group Discrimination*

Variable	Group	Mean	Sample size	Standard deviation	Test statistic (t or z)
Total cholesterol	MI	331.47	23	82.49*	2.78‡
	N	280.85	59	45.78	
β cholesterol	MI	219.84	24	74.46*	2.26§
	N	183.32	58	42.06	
Lipid P	MI	11.821	23	2.446*	2.46§
	N	10.463	58	1.590	
$\frac{\beta\ cholesterol}{Total\ cholesterol} \times 100$	MI	65.31	23	11.69*	.18
	N	64.83	58	7.32	
S_f^o 0-400	MI	724.25	24	222.50†	3.47‖
	N	551.71	59	156.45	
S_f^o 0-12	MI	489.8	24	155.7*	3.17‡
	N	381.9	59	92.8	
S_f^o 12-20	MI	65.7	24	37.1*	2.20§
	N	47.9	59	22.5	
S_f^o 20-400	MI	168.75	24	117.95	1.94
	N	121.90	59	91.72	
Atherogenic index	MI	87.88	24	28.93	3.35‖
	N	67.92	59	22.65	
$\frac{Cholesterol}{Lipid\ P}$	MI	27.98	23	3.42	1.40
	N	26.93	58	2.88	

* MI standard deviation significantly different from the normal standard deviation at the .01 level.

† MI standard deviation significantly different from the normal standard deviation at the .05 level.

‡ MI mean significantly different from the normal mean at the .01 level.

§ MI mean significantly different from the normal mean at the .05 level.

‖ MI mean significantly different from the normal mean at the .001 level.

parameter have been accomplished by alcohol fractionation methods and paper electrophoresis. The value for percentage of total cholesterol borne by the β-lipoprotein fraction reported here (66 per cent) compares favorably with the values reported by persons using alcohol fractionation techniques (66 per cent by Oncley et al.,[13] 69 per cent by Barr et al.,[14] 70 per cent by Pearsall and Chanutin[15]). Using paper electrophoresis, Nikkila[16] reported a value of 64 per cent for β-cholesterol, while Durrum's[17] value, also with paper electrophoresis methods, was approximately 80 per cent.

Results and Discussion

The data for the serum parameters are summarized in table 1.

Each variable was considered separately. A test of homogeneity of variances was performed on the N and MI groups to see if their variances were essentially equal. If this test indicated no significant difference, a t test (which assumes equal group variances and a normal distribution for each group) was used to test for differences in mean values. If the homogeneity of variance procedure showed significant difference, a z test, assuming normal distribution for each group but not equal group variances, was performed. The hypothesis tested on each variable was that "the means for the 2 groups were sampled from the same population."

The only parameters in table 1 for which the differences of the means of the 2 groups are significant at the 0.001 level are S_f^o 0-400 lipoprotein concentrations and the calculated atherogenic index. No individual lipoprotein class concentration measured showed a significant difference between the 2 groups at the .001 level as did the sum of all the β-lipoprotein concentrations, although the means of the N and MI groups for each separate class were significantly separated.*

The data indicate a decrease with decreasing lipoprotein density (higher S_f^o value) of the level of significance for differences in mean value between the 2 groups. In the Gofman atherogenic index, greater weighting is given to the lipoprotein moieties with higher S_f^o values. Also, S_f^o 0-400 lipoprotein concentration, with no weighting of any component class, is at the same level of significance as the atherogenic index. Both these factors indicate that a re-evaluation of the weighting factors in the calculation of the atherogenic index might lead to a more sensitive parameter.

Total cholesterol discriminates between the 2 groups at a level of significance (0.01) less than either S_f^o 0-400 concentration or atherogenic index (0.001), although cholesterol concentration is better than any of the other lipid parameters. Since only the β-lipoproteins are included in the calculation of the atherogenic index, it would seem that a measurement of β-cholesterol might be more effective than one of total cholesterol. Such

*In the case of S_f^o 20-400, the value for t is on the threshold of significance at the 0.05 level.

s not the case; β-cholesterol differentiates between the 2 groups at the 0.05 level of significance. These data indicate that some importance must be ascribed to the protein components of the lipoprotein moieties.

More significant discrimination of the β-lipoprotein parameters between diseased and normal persons may be due to the nature of the lipid-protein bond or the relative concentrations of the various constituents in the lipid-protein complex. These explanations do not require that any single lipid variable differentiate as well as the β-lipoproteins, but it would be expected that the lipid variables would show some significant separation between groups.

Neither the ratios of β to total cholesterol nor of total cholesterol to lipid phosphorus seem to discriminate the groups. The significance attached to the component parameters disappears when they are combined into a ratio.

It must be emphasized that these data (as well as most of the literature on this subject) relate to the ability of a serum parameter to discriminate between *groups* of MI and N subjects. The extrapolation of such data to the individual as a predictive measure is unwarranted except for calculation of the risk or of probability of disease in relation to other persons of the same age group. It may be, for instance, that the change in serum characteristics of the diseased patient, which well could account for the difference observed here, occurs after clinical manifestation of the disease. Only a "before and after" clinical study can accomplish an evaluation of "predictive" as opposed to "discriminatory" efficiency for any set of variables. Until such a clinical study is completed, any serum lipid or lipoprotein determination on an individual is only of incidental interest. Such a study, of the West Point class of 1956,[18, 19] is in progress in this laboratory.

Summary

Several serum parameters were evaluated as discriminators between a normal (N) and a coronary disease (MI) group. The best discriminating parameters were S_f^0 0-400 lipoprotein concentrations and the calculated atherogenic index. The means of the N and MI groups for each lipoprotein class were significantly separated. Total cholesterol was a less effective discriminator than total β-lipoprotein concentration or atherogenic index, but more effective than β-cholesterol or lipid phosphorus.

The data indicate that (a) some importance must be ascribed to the protein components of the lipoprotein moieties, and (b) a re-evaluation of the weighting factors in the calculated atherogenic index might lead to a more sensitive parameter.

Acknowledgment

The authors gratefully acknowledge the statistical assistance of Alton J. Rahe, Department of Biometrics, School of Aviation Medicine, USAF.

Summario in Interlingua

Plure parametros serologic esseva investigate con respecto a lor valor como criterios del differentiation de un gruppo de subjectos normal (N) ab un gruppo de subjectos con morbo coronari (MI) Le parametros le plus fidel pro ille differentiation esseva (1) le concentrationes de lipoproteina S_f^0 0-400 e (2) le calculate indice atherogenic. Le valores medie pro omne le classes de lipoproteina esseva significativemente differente in le duo gruppos, i.e. le gruppo N e le gruppo MI. Le valor del cholesterol total esseva un minus efficace differentiator que le valor de lipoproteina beta o le indice atherogenic. Del altere latere, illo esseva un plus efficace differentiator que le valor de cholesterol beta o le valor de phosphoro lipidic.

Le datos indica (a) que un certe importantia debe esser ascribite al componentes proteinic in le subdivisiones de lipoproteina e (b) que un re-evalutation del factores de ponderation in le calculation del indice atherogenic poterea resultar in le obtention de un parametro de plus alte grados de sensibilitate.

REFERENCES

1. Gofman, J. W., Lindgren, F., Elliot, H., Mantz, W., Hewitt, J., Strisower, B., and Herring, V.: The role of lipids and lipoproteins in atherosclerosis. Science **111**: 166, 1950.
2. Editorial: Experimental studies on etiology of atherosclerosis. J.A.M.A. **143**: 1344, 1950.
3. Gertler, M. M., and Garn, S. M.: Lipid interrelationship in health and in coronary artery disease. Science **112**: 14, 1950.
4. Oliver, M. F., and Boyd, G. S.: Serum lipoprotein patterns in coronary sclerosis and associated conditions. Brit. Heart J. **17**: 299, 1955.
5. Lewis, L. A., and Page, I. H.: Ultracentrifuge and electrophoretic studies on serum lipoproteins in relationship to vascular disease. Circulation **2**: 466, 1950.
6. Gertler, M. M., Garn, S. M., and White, P. D.: Young candidates for coronary heart disease. J.A.M.A. **147**: 621, 1951.
7. Report of a cooperative study of lipoproteins and atherosclerosis: Evaluation of serum lipoprotein and cholesterol measurements as predictors of clinical complications of atherosclerosis. Circulation **14**: 691, 1956.
8. Gofman, J., Strisower, B., deLalla, O., Tamplin, A., Jones, H., and Lindgren, F.: Index of coronary artery atherogenesis. Modern Med. **11**: 119, 1953.
9. Redmond, R. F., Milch, L. J., Calhoun, W. W., Chinn, H. I., and the Cardiovascular Research Group: The evaluation of clinical tests for atherosclerosis. I. Instrumentation. School of Aviation Medicine, USAF, Project no. 21-32-027, Report no. 1, Aug. 1952.
10. Milch, L. J., Calhoun, W. W., and Redmond, R. F.: The evaluation of clinical tests for atherosclerosis. Improved techniques in ultracentrifugal analysis. School of Aviation Medicine, USAF, Project no. 21-1601-0007, Report no. 2, Aug. 1953.
11. deLalla, O. F., and Gofman, J. W.: Ultracentrifugal analysis of serum lipoproteins. *In* Methods of Biochemical Analyses. *Glick*, D., ed. New York, Interscience Publishers, Inc., p. 459.
12. Redmond, R. F., Milch, L. J., Calhoun, W. W., Chinn, H. I., and the Cardiovascular Research Group: Biochemical and biophysical methods in cardiovascular research. Texas Rep. Biol. & Med. **11**: 83, 1953.
13. Oncley, J. L., Gurd, F. R. N., and Melin, M.: Preparation and properties of serum and plasma proteins. XXV. Composition and properties of human serum β-lipoprotein. J. Am. Chem. Soc. **72**: 458, 1950.
14. Russ, E. M., Eder, H. A., and Barr, D. P.: Protein-lipid relationships in human plasma. Am. J. Med. **11**: 468, 1951.
15. Pearsall, H. R., and Chanutin, A.: Electrophoretic, nitrogen and lipide analyses of plasma and plasma fractions of healthy young men. Am. J. Med. **7**: 297, 1949.
16. Nikkila, E.: Studies on the lipid-protein relationships in normal and pathological sera and the effect of heparin on serum lipoproteins. Scandinav. J. Clin. & Lab. Invest. 5, suppl. 8, 1953.
17. Langam, T. A., Durrum, E. L., and Jenks, W. P.: Paper electrophoresis as a quantitative method: Measurement of α and β-lipoprotein cholesterol. J. Clin. Invest. **34**: 1427, 1955.
18. Milch, L. J.: Military aspects of coronary artery disease. Mil. Surgeon **114**: 333, 1954.
19. —, Taylor, W. F., Schlessinger, B. S., Hughes, H. M., Redmond, R. F., Weiner, N., Calhoun, W. W., and Yarnell, R. A.: Cardiovascular evaluation of West Point cadets: A four-year report. Mil. Med. **122**: 332, 1958.

Cardiac Chamber Volumes and their Significance in Rheumatic Heart Disease with Isolated Mitral Stenosis

By Louis A. Soloff, M.D., and Jacob Zatuchni, M.D.

The total capacity of the heart and the volume of each of its chambers were determined by the technic of simultaneous biplane stereoscopic venous angiocardiography in 18 persons with surgically confirmed, isolated severe mitral stenosis. Although cardiac capacity and chamber volumes varied greatly, the left atrium was almost always the largest chamber. The left ventricle was not always the smallest chamber. In fact, it was larger than the right ventricle in 7 of the 18 and was the only chamber to be significantly correlated with total cardiac capacity greater than 1,000 ml. The right ventricular volume was found to be significantly correlated with its systolic pressure, or with the pulmonary artery systolic or mean pressures. Disproportionate enlargement of the right atrium can occur in the absence of tricuspid stenosis. Finally, atrial fibrillation was commonly present in patients with a large total cardiac capacity.

ROENTGENOLOGIC measurements of the heart should ideally provide information concerning the volume of its chambers and the thickness of its walls during various phases of the cardiac cycle. Such information is as yet not available. Nevertheless, all measurements, whether linear, planigraphic, or volumetric, have meaning only insofar as they approximate this ideal information. Measurements of the heart on conventional roentgenograms are concerned with over-all size of the cardiac silhouette. These measurements combined with the shape of the cardiac silhouette are used to judge size of the chambers and to a lesser extent thickness of its walls . Such deductions are not inherent in the roentgenogram itself but are based upon years of study by physicians who correlated roentgenographic findings with anatomic specimens. There are, however, gross differences between the anatomic specimen and the cardiac silhouette. There are changes in position and in plasticity, but most important the anatomic specimen is devoid of the intracardiac pressures that are so important in molding the shape and size of the cardiac chambers. It is equally difficult to visualize the interlocking relationships of the chambers in the anatomic specimen. It is for these reasons that precise knowledge of the size of the cardiac chambers is not obtainable from study of either the conventional roentgenogram or the anatomic specimen. For instance, we have previously demonstrated that esophageal displacement fails to define the degree of left atrial enlargement, that the small aorta in mitral stenosis may be an illusion, and that the left atrium may be strikingly enlarged in diseases affecting predominantly the left ventricle.[1-3] This knowledge was obtained by angiocardiography, a technic that makes possible visualization of individual chambers and the thickness of their walls.

We now propose to employ this technic to determine the volume of the cardiac chambers in rheumatic heart disease with isolated mitral stenosis.

Materials and Methods

Eighteen persons with inactive rheumatic heart disease and isolated mitral stenosis were studied preoperatively. The criteria for the diagnosis of isolated mitral stenosis have been described elsewhere.[4] Severe mitral stenosis was found in each person at surgery. Mitral regurgitation and other valvular lesions were not detected. There were 15 females, 20 to 49 years old, and 3 males, 33 to 48 years old. Ten had normal sinus rhythm and 8 had atrial fibrillation. None had clinical evidence of cardiac failure when studied. Cardiac catheterization was done in 17 and revealed no evidence of a gradient across the tricuspid valve.

From the Department of Medicine, Temple University Medical School and Hospital, Philadelphia, Pa.
Supported in part by a grant from the Heart Association of Southeastern Pennsylvania.

TABLE 1.—*Volume of Each Cardiac Chamber in Persons with Rheumatic Heart Disease and Isolated Mitral Stenosis Arranged According to Total Cardiac Capacity*

Subject	Sex	Age	NSR*	AF†	Mitral orifice	Right atrium: Systolic pressure (mm.)	Right ventricle: Systolic pressure (mm.)	Right ventricle: Diastolic pressure (mm.)	Pulmonary artery: Systolic pressure (mm.)	Pulmonary artery: Mean pressure (mm.)	Pulmonary capillary venous pressure (mm.)	Chamber volume (ml.): Right atrium	Right ventricle	Left atrium	Left ventricle	Total cardiac capacity (ml.)
1. W.D.	F	33	+		5 × 2 mm.	5	85	—6	64	39	34	96	117	269	113	595
2. J.P.	F	22	+		2 × 3 mm.	2	34	4	30	20	17	131	166	209	96	602
3. M.D.	F	20	+		Pencil	5	30	11	31	20	24	130	123	232	139	624
4. F.K.	F	42		+	Match-stick	10	50	8	52	41	37	166	95	259	149	669
5. E.S.	M	41	+		< 1 finger	10	55	8	52	40	24	186	69	352	133	740
6. E.H.	F	42		+	Cigarette	—	—	—	—	—	—	153	89	335	184	761
7. C.P.	F	28	+		String-like bands	1	64	2	53	45	16	241	156	277	96	770
8. L.N.	F	45		+	Tip	10	49	12	43	30	18	147	148	347	150	792
9. M.T.	F	39	+		8 × 3 mm.	4	65	2	56	39	18	237	233	295	41	806
10. T.H.	F	32	+		7 × 2 mm.	10	50	8	52	41	37	237	171	236	172	816
11. S.N.	F	36	+		Markedly contracted	13	68	14	72	40	38	139	202	400	75	816
12. I.A.	F	45		+	Markedly contracted	6	25	6	26	20	17	114	174	514	90	892
13. M.I.	F	26	+		5 mm.	10	45	0	48	30	27	119	63	562	194	938
14. J.C.	F	33		+	4 × 4 mm.	7	48	10	67	42	20	138	192	551	100	981
15. T.J.	M	48	+		2 matches	7	121	7	112	72	31	269	282	277	122	1250
16. L.D.	M	33		+	Tip	10	32	8	28	18	8	395	165	567	145	1272
17. E.M.	F	41		+	< 1 cm.	11	43	0	53	33	15	300	258	550	207	1315
18. K.C.	F	49		+	Tip	7	86	8	86	59	40	244	311	582	204	1341

*Normal sinus rhythm.
†Atrial fibrillation.

Simultaneous biplane (posteroanterior and left lateral) stereoscopic venous angiocardiograms, at a tube-to-film distance of 100 cm., were obtained every 0.7 second for at least 30 exposures. The duration of each exposure was 0.1 second.

The maximal size of each of the cardiac chambers was obtained by determining its outermost limits on the sequential venous angiocardiograms and reconstruction by tracing on onionskin paper.

Area of each of the cardiac chambers in the frontal plane was determined by use of a compensating polar planimeter. Depth is the largest diameter of the chamber in the lateral projection, perpendicular to the frontal plane. Volume of each cardiac chamber is the product of the area in the frontal plane and the depth in the lateral plane.

Other methods for determination of volume were also used. These included (1) the product of the area in the lateral plane and the diameter in the frontal plane, (2) the product of the areas in the frontal and lateral planes raised to the ¾ power, and (3) the sum of volumes of small cylindrical components of each of the chambers in both planes. These technics were discarded, following study of all subjects, in favor of the method given because of (1) difficulty in determining in the frontal plane a single representative diameter, (2) prejudice in using product of areas of an assumed common diameter, and (3) unequal projection of areas in both planes, which makes the creation of equivalent cylinders impossible in this type of cardiac disease. The method used is similar to that conventionally employed to determine volume of the cardiac silhouette.[5]

No correction factor for distortion produced by a tube-to-film distance of 100 cm. was used because of difficulty, if not impossibility, of obtaining

equally important measurements inherent in its calculation. A factor to correct for distortions of volume produced by shape was also not employed because either the chamber did not conform significantly with any known geometric figure that could be analyzed mathematically or, regardless of similarity to a geometric structure in 1 plane, its entire shape and uniformity could not be determined even from 2 projections. Parenthetically, it can be stated that even for the heart as a whole, we have not encountered a mathematician who agrees with the usual statement that the heart is suggestive of a "combined sphere and a transversally placed paraboloid" and who is willing to accept Rohrer's correction factor of 0.63 or any other mathematical equation based on similar assumptions of shape.

For all these reasons, we have preferred to report each chamber volume as the product of its area in the frontal plane and greatest linear diameter perpendicular to it. Total cardiac volume, as used in this study, is the sum of the volumes of the 4 chambers. Obviously, it is representative of capacity rather than total cardiac volume, for solid mass is not included in its measurement.

Results

Table 1 gives the actual volume of each of the cardiac chambers arranged according to total cardiac capacity. Total cardiac capacity varied greatly and showed no significant relationship either to age or to duration of rheumatic heart disease. Atrial fibrillation was correlated best with total cardiac capacity and was more frequent the larger the total cardiac capacities.

Chamber volumes and their relationship to each other also varied greatly. No significant relationship was found between the right atrial volume and its pressure, or between the right ventricular volume and either its end-diastolic pressure or the mean pulmonary capillary venous pressure. A suggestive relationship was found between the right ventricular systolic pressure and its volume ($r = 0.4657$, $p > 0.05$). Further study, however, showed that there was no relationship between these 2 variables with observed values of right ventricular volume less than 165 ml. ($r = 0.1655$, $p > 0.70$) and a significant one with observed values of 165 ml. or more ($r = 0.7716$, $p < 0.01$). Such right ventricular volumes were also significantly correlated with the pulmonary artery systolic pressure ($r = 0.7771$, $p < 0.01$) and with the pulmonary artery mean pressure ($r = 0.7857$, $p < 0.01$).

The volume of the left atrium was almost always larger than that of any other cardiac chamber. It constituted 28.9 to 59.9 per cent of the total cardiac capacity. There was a tendency for the larger total cardiac capacities to be associated with larger left atrial volumes that were frequently disproportionately increased. However, a small total cardiac capacity did not exclude a large left atrium. Conversely, a large total cardiac capacity did not exclude a relatively small left atrium.

The left ventricular volume was the smallest of the chamber volumes in only 55.6 per cent and was larger than the right ventricular volume in 38.9 per cent.

Finally, a significant relationship was demonstrated between the total cardiac capacity and the volume of each chamber except the left ventricle. However, if the total cardiac capacity was less than 1,000 ml., it was significantly correlated only with the left atrial volume and if greater than 1,000 ml. only with the left ventricular volume. The correlation coefficients and their probabilities may be seen in table 2.

Discussion

These findings indicate that the left atrium is almost always the largest chamber of the heart of a person with rheumatic heart disease and isolated mitral stenosis. This fact has been generally assumed but has not actually been previously demonstrated during life. This chamber may at times occupy more than half the total capacity of the heart. The corollary of this statement is that the left atrium does not empty completely in systole and must indeed have the greatest residual systolic volume of all the cardiac chambers, a fact readily demonstrable by angiocardiography. Indeed, if this chamber is very large, there may be no appreciable change in its outer contour during various phases of the cardiac cycle. In fact, we have been unable to detect, by high-speed cinematographic stud-

TABLE 2.—*Correlation Coefficients and Their Probabilities for Total Cardiac Capacity and Chamber Volumes*

	Right atrium	Right ventricle	Left atrium	Left ventricle
Total cardiac capacity	$r = 0.7083^*$ $p < 0.01$	$r = 0.6845^*$ $p < 0.01$	$r = 0.8748^*$ $p < 0.001$	$r = 0.4108$ $p > 0.05$
Total cardiac capacity less than 1,000 ml.	$r = 0.0949$ $p > 0.70$	$r = 0.2399$ $p > 0.40$	$r = 0.8521^*$ $p < 0.001$	$r = 0.0175$ $p > 0.90$
Total cardiac capacity greater than 1,000 ml.	$r = 0.4124$ $p > 0.50$	$r = 0.4479$ $p > 0.50$	$r = 0.0534$ $p > 0.90$	$r = 0.9581^*$ $p < 0.05$

*Significant.

ies, any motion of the lateral and cephalic borders of the left atrium in the lateral projection.[6] Emptying of the left atrium under these circumstances is accomplished for practical purposes entirely by the piston-like action of the atrioventricular valves.

There is, however, no constant relationship in isolated mitral stenosis between the volume of the left atrium and that of the other cardiac chambers. Thus, the ratio of the volume of the left atrium to that of the right ventricle varied from 1.2 to 8.9, a 7-fold difference. Wide variation was also found when the left atrial volume was related to that of the right atrium or to the combined volumes of the right atrium and right ventricle. Such marked variation strongly supports the view that no single factor is equally effective in the production of enlargement of the left atrium, right ventricle, and right atrium. Back pressure from mitral block is obviously inadequate by itself to explain this variation.

We have previously reported that left atrial volume in isolated mitral stenosis cannot be correlated significantly with any pressure parameter, or with age or duration of the rheumatic state.[4] On the other hand, we have also reported that pulmonary artery size does correlate significantly with the mean pulmonary artery pressure.[2] We report now a significant correlation between the right ventricular systolic pressure and its volume for observed values of 165 ml. or more, and also between such volumes and the pulmonary artery systolic and mean pressures.

The demonstration of disproportionate enlargement of the right atrium in the absence of tricuspid stenosis raises serious doubt of the reliability of this sign which has been so used by others.[7] Conceivably, it may be due to tricuspid incompetency not ordinarily detectable but suggested by the finding of an elevated right atrial pressure.[8] It may also represent change in elasticity either primary or secondary to bouts of hypervolemia or both, for a significant correlation was found between the volume of the right atrium and total cardiac capacity but not between it and its pressures.

The interplay of these various factors in the production of chamber enlargement is also demonstrated by their relationship to right ventricular volume. Here, a significant relationship was found between the total cardiac capacity and the volume of the right ventricle. Yet, increase in the latter above 165 ml. is, as stated before, also significantly related to its pressure.

For these reasons, it appears that pressure, change in elasticity, and hypervolemia act variably and do not uniformly affect the entire heart. Moreover, they do not necessarily act together during all phases of the life cycle of rheumatic heart disease. Thus, the fact that the total cardiac capacity when less than 1,000 ml. correlates only with the left atrial volume is readily understandable, if enlargement of the left atrium occurs first and is, thereby, the major cause for increasing the total capacity of the heart. Right ventricular enlargement, on the other hand, is partly dependent upon

pulmonary artery pressure, which is not related to left atrial volume. Finally, the left ventricle may not be significantly enlarged until hypervolemia is or has been present. Hypervolemia may also disproportionately distend the left ventricle because the elasticity of the other chambers has been seriously compromised. This may be the reason that the total cardiac capacity when greater than 1,000 ml. correlates only with the left ventricular volume.

Perhaps for these reasons, left ventricular volume in severe mitral stenosis is not invariably decreased. In one half of the group, it was 150 ml. or more. Moreover, it is not always the smallest chamber of the heart in mitral stenosis, for in 7 of the 18, it was larger than the right ventricle. It is also possible that the left ventricle may be slightly enlarged in mitral stenosis because mitral regurgitation was present during the initial phase of rheumatic heart disease[9] and reappears or increases whenever resistance to left ventricular forward flow is temporarily increased.

Summary and Conclusions

A study was made of 18 persons with rheumatic heart disease and isolated severe mitral stenosis, confirmed at surgery, to determine the volume of each of the cardiac chambers opacified by the technic of simultaneous biplane stereoscopic venous angiocardiography.

The volume of each chamber is represented by the product of the area in the frontal plane and the greatest linear diameter perpendicular to it. Total cardiac capacity is the sum of the chamber volumes.

Each of the chambers varied greatly in volume, right atrium 96 to 395 ml., right ventricle 63 to 311 ml., left atrium 209 to 582 ml., and left ventricle 41 to 207 ml. Total cardiac capacity varied from 595 to 1,341 ml.

Almost always the volume of the left atrium exceeded that of the other chambers, and constituted 28.9 to 59.9 per cent of the total cardiac capacity.

Wide variation was found between the volume of the left atrium and that of the right ventricle or right atrium or both.

Disproportionate increase in volume of the right atrium not due to tricuspid stenosis may occur in severe mitral stenosis.

The volume of the left ventricle varied 5 fold, was not invariably small, and, indeed, was not always the smallest chamber.

A significant relationship was found between the right ventricular volume for observed values of 165 ml. or more and its systolic pressure, and also with the pulmonary artery systolic and mean pressures.

A significant correlation was demonstrated between the total cardiac capacity and the volume of each chamber except the left ventricle. However, if the total cardiac capacity was less than 1,000 ml., it was significantly correlated only with the left atrial volume, and, if greater than 1,000 ml., only with the left ventricular volume.

Finally, the larger total cardiac capacities were commonly associated with atrial fibrillation.

Acknowledgment

We thank Professor Walter G. Lawton, Head of the Department of Mathematics, Temple University, for his mathematical guidance, and Herman Siplet, B.S., Fels Foundation, Temple University, for his statistical analysis. We also thank George E. Mark, Jr., M.D., Associate Professor of Medicine, Temple University School of Medicine, for the data obtained by cardiac catheterization.

Summario in Interlingua

Esseva effectuate un studio de 18 patientes con rheumatic morbo cardiac e isolate stenosis mitral de grado sever, chirurgicamente confirmate, con le objectivo de determinar le volumine de cata un del cameras cardiac opacificate per le technica de veno-angiocardiographia biplan-stereoscopic simultanee.

Le volumine de omne camera individual es representate per le producto del area in le plano frontal con le plus grande diametro linear perpendicular a ille plano. Le capacitate cardiac total es le summa del volumines del cameras.

Le volumine de cata un del cameras variava grandemente: le atrio dextere ab 96 a 395 ml, le ventriculo dextere ab 63 a 311 ml, le atrio sinistre ab 209 a 582 ml, e le ventriculo sinistre

ab 41 a 207 ml. Le capacitate cardiac total variava ab 595 a 1341 ml.

In quasi omne casos, le volumine del atrio sinistre excedeva le volumine del altere cameras. Illo constitueva inter 28,9 e 59,9 pro cento del total capacitate cardiac.

Extense variationes esseva constatate in le relation inter le volumine del atrio sinistre e le volumine del ventriculo dextere o del dextere o de ambes.

Augmentos disproportional in le volumine del atrio dextere, non causate per stenosis tricuspidal, pote occurrer in casos sever de stenosis mitral.

Le volumine del ventriculo sinistre variava usque a un maximo 5 vices plus grande que le minimo. Illo non esseva invariabilemente micre. De facto, illo non esseva le plus micre del cameras in omne le casos studiate.

Esseva constatate un relation significative inter le volumine dextero-ventricular a nivellos de 165 ml o plus e le correspondente pression systolic o, similemente, le pressiones pulmono-arterial systolic e medie.

Esseva demonstrate un correlation significative inter le capacitate cardiac total e le volumine del cameras individual, con le exception del ventriculo sinistre. Tamen, in casos in que le capacitate cardiac esseva minus que 1000 ml, illo esseva correlationate significativemente con solmente le volumine del atrio sinistre, e quando illo esseva plus que 1000 ml, illo esseva correlationate significativemente con solmente le volumine del ventriculo sinistre.

Finalmente, le major capacitates cardiac total esseva communmente associate con fibrillation atrial.

REFERENCES

1. Soloff, L. A., and Zatuchni, J.: The relationship of displacement of the esophagus to left atrial volume and heart size in persons with mitral stenosis. Am. J. Med. **21**: 551, 1956.
2. —, —, Mark, G. E., Jr., and Stauffer, H. M.: The size of the pulmonary artery in rheumatic heart disease with isolated mitral stenosis. Am. J. M. Sc. **234**: 313, 1957.
3. —, —, Stauffer, H. M., and Kelly, E. W.: Angiocardiographic observations of intracardiac flow in the normal and in mitral stenosis. Circulation **13**: 334, 1956.
4. —, —, and Mark, G. E., Jr.: Relationship of left atrial volume to pulmonary artery and wedge pressures in mitral stenosis. Circulation **15**: 430, 1957.
5. Friedman, C.-E.: Heart volume, myocardial volume and total capacity of the heart cavities in certain chronic heart diseases. Acta med. scandinav. suppl. **257**: 1951.
6. Soloff, L. A., Zatuchni, J., and Stauffer, H. M.: Unpublished observations.
7. Goodwin, J. F., Rab, S. M., and Zoob, M.: Rheumatic tricuspid stenosis. Brit. M. J. **2**: 1383, 1957.
8. Muller, O., and Shillingford, J.: Tricuspid incompetence. Brit. Heart J. **16**: 195, 1954.
9. Wilson, M. G., and Lim, W. N.: The natural history of rheumatic heart disease in the third, fourth and fifth decades of life. 1. Prognosis with special reference to survivorship. Circulation **16**: 700, 1957.

CLINICAL PROGRESS

Beriberi Heart Disease

By REVERDY H. JONES, JR., M.D.

Two cases of beriberi heart disease are presented together with a discussion of the history, diagnosis, and treatment of this condition. Special emphasis is given to the broadened concept of the diagnosis of beriberi heart disease, particularly as it occurs in the Occident.

DURING THE PAST several decades significant advances have been made in the diagnosis and therapy of various types of heart disease. Intensive investigative studies have now assigned specific causes to certain cardiac disorders that formerly, for want of a more accurate classification, were loosely grouped under the category of "arteriosclerotic," "coronary," or "idiopathic" heart disease. Beriberi heart disease is one such abnormality and it is the purpose of this communication to describe the clinical manifestations, the diagnosis, and the treatment of this condition as illustrated by 2 cases.

Although classical descriptions of the polyneuritic form of beriberi have been available in Japanese and Chinese literature for many centuries, it was not until 1929 that Aalsmeer, a Javanese physician, and Wenckebach[1] presented an adequate description of the cardiovascular manifestations of this disorder. These authors emphasized the bounding pulse, pistol-shot sounds over the larger arteries, predominant right heart failure, venous engorgement, and frequent syncope and shock They thought that there was peripheral vasodilatation, described the rapid circulation, and noted that improvement often occurred after the administration of thiamine. It has been this striking symptomatology as described in the Orient which has, until recently, dominated the clinical impression of beriberi heart disease.

While sporadic reports of cardiac manifestations in beriberi appeared in the United States from 1925 to 1928,[2, 3] the relationship of thiamine deficiency to the cardiovascular manifestations of this disease, as found in this country, was not fully appreciated until the investigations of Weiss and Wilkins in 1936.[4] These authors described 97 patients with "wet beriberi," all of whom had been on vitamin B_1-deficient diets and most of whom were chronic alcoholics, and concluded that the same types of beriberi described in the Orient existed in this country. Like Aalsmeer and Wenckebach, they emphasized the clinical manifestations of rapid circulation in the presence of heart failure. However, left ventricular failure with dyspnea, orthopnea, and pulmonary congestion were observed as often as pure right-sided failure. A predilection to circulatory collapse and shock was noted, particularly in the presence of respiratory infections. Severe polyneuritis was found only in cases of mild congestive failure. In some patients electrocardiographic changes with tachycardia but without other abnormalities were seen. Weiss and Wilkins[5] concluded that the "cardiovascular disturbances caused by nutritional defects do not form a rigid clinical syndrome."

In 1945 Blankenhorn[6] of Cincinnati commented on the few references to the cardio-

From the Medical Department, Lewis-Gale Hospital, Roanoke, Va.

Presented, in part, at the Regional Meeting, American College of Physicians, Richmond, Va., February 1956.

vascular manifestations of beriberi in this country and stated that the condition was not at all rare in hospitals where other deficiency diseases occurred. He thought that too strict adherence to the criteria of beriberi heart disease as described by Aalsmeer and Wenckebach had much to do with the failure to observe this disorder more frequently, and he stated that the well-known Oriental concept of the disease probably hindered rather than helped to establish the diagnosis in many cases in the United States. Keefer[7] in 1930, in describing cases of beriberi heart disease in Peiping, China, found that only 30 per cent exhibited a rapid circulation. Goodhart and Jolliffe[8] in studying the cardiovascular complications in chronic alcoholism observed no acceleration of the circulation or conspicuous enlargement of the right heart. Blankenhorn also thought that rapid peripheral circulation and prominence of the right heart were often absent in the Occidental type of beriberi heart disease. In an effort to facilitate the diagnosis of beriberi heart disease, Blankenhorn proposed the following criteria:[6] (1) enlarged heart with normal (sinoatrial) rhythm, (2) dependent edema, (3) elevated venous pressure, (4) peripheral neuritis or pellagra, (5) nonspecific changes in the electrocardiogram, (6) no other cause evident, (7) gross deficiency of diet for 3 months or more, and (8) improvement and reduction of heart size after specific treatment or autopsy findings consistent with beriberi.

Following this expansion of the criteria for the diagnosis of beriberi heart disease by Blankenhorn,[6] many more case reports appeared in the literature.[9-12] Some of these cases have failed to fulfill even the above criteria. Dock[13] particularly commented on the great variety of clinical findings in beriberi, depending upon the region, type, and habits of the patients studied. Hussey and Katz[14] concluded that the symptoms and signs of beriberi heart disease show no important variation from those of heart failure due to other causes, and therefore the diagnosis depends mainly upon evidence of a deficient diet, on the exclusion of other etiologic types of heart disease, and on the therapeutic response to the administration of thiamine chloride.

Thus since the original description, the concept of beriberi heart disease has become considerably broadened. Although the originally described Oriental cases and some of the cases in the United States demonstrate the picture of hyperkinetic circulation in the presence of congestive failure, many other cases fail to present this vivid picture. Occidental beriberi heart disease is undoubtedly more prevalent than the number of cases diagnosed at the present time would seem to indicate.

Etiology

Considerable evidence indicates that thiamine deficiency is the primary etiologic factor. Cardiac disturbances produced in animals fed by thiamine-deficient diets disappear following the administration of thiamine chloride.[15] Likewise, electrocardiographic abnormalities similar to those observed in beriberi can be produced by giving a thiamine-deficient diet to healthy persons; these changes return to normal following the restoration of an adequate diet.[16] Thiamine is essential in carbohydrate metabolism, and consequently the amount of carbohydrate in the diet is an important contributing factor in the pathogenesis of beriberi.[17] That an increase in carbohydrate consumption may predispose to beriberi by increasing the metabolic demands for vitamin B_1 is shown by the consistent inability to produce thiamine deficiency in pigeons on a vitamin B_1-deficient diet that is high in fats rather than carbohydrates.[10]

In the Orient beriberi occurs primarily in those individuals whose chief food is polished rice, which is deficient in thiamine but high in carbohydrates. In the Occident beriberi heart disease occurs chiefly in chronic alcoholics. Alcohol, like polished rice, is particularly low in vitamin B_1, but has a high carbohydrate content. That alcohol itself is a contributing rather than a primary cause of the cardiovascular manifestations of beriberi has been proved[18] by the complete reversal of the clinical picture following the administration of large doses of thiamine to patients

who maintain their usual intake of alcohol. Physical exertion is likewise a contributing factor; cardiac manifestations of beriberi are more frequent and more rapidly produced by regimes of strenuous physical exertion. Some of the cardiovascular characteristics of thyrotoxicosis and of pregnancy may be caused in part by the increased thiamine requirement. Similarly, infectious diseases, particularly pneumonia, with their increased thiamine requirements, may precipitate fulminating beriberi in subclinical, deficient individuals. Another etiologic factor may be faulty gastrointestinal absorption of vitamin B_1 due to chronic gastrointestinal disease and occasionally following operation.

Finally, and quite important, thiamine deficiency may influence the course of other etiologic types of heart disease, a fact recognized by Weiss as early as 1936.[4] Some of the signs and symptoms in such patients may be caused by a coexistent vitamin B_1 deficiency rather than by the primary cardiac abnormality itself.

Signs and Symptoms

The clinical manifestations of beriberi heart disease vary considerably with the severity and rapidity of the onset of the condition. The signs and symptoms of heart failure are most frequent. The picture of the severely dyspneic, flushed, orthopneic, diffusely edematous patient as commonly described in the Orient has already been discussed. Such patients may be observed in the United States and may develop syncope and shock, with sudden death.

In the Occidental type of beriberi heart disease, however, the clinical manifestations are not usually so dramatic. Dyspnea, weakness, swelling of the ankles, and a nonproductive nocturnal cough are the most common complaints. Examination of the heart reveals tachycardia, gallop rhythm, and often a systolic and less frequently a soft diastolic murmur that may lead to the diagnosis of incompetency of the aortic valve. With treatment and relief of the decompensation these murmurs disappear. There is usually moderate dependent edema, enlarged liver, and prominent and engorged veins. The systolic blood pressure is often slightly elevated and in the more severe cases the pulse pressure is decreased and pistol-shot sounds are heard over the large arteries. The circulation time may be shortened, but is usually moderately prolonged. In the 22 cases reported by Benchimol and Schlesinger,[10] for example, 11 had a prolonged circulation time; in the other 11, the circulation time was normal.

X-ray of the chest usually reveals cardiac enlargement with prominence of both the left and right ventricles and pulmonary congestion; on fluoroscopy, cardiac pulsations can be readily distinguished and the cardiac shadow may be differentiated from pericardial effusion. Pleural effusion is not uncommon.

Nonspecific electrocardiographic changes are common though not necessarily constant in occurrence. The main abnormalities consist in low voltage or inversion of the T waves and prolongation of the Q-T interval. Low voltage of the ventricular complex occurs and, although conduction defects are rare, bundle-branch block has occasionally been reported.[9-19] Significant arrhythmias are characteristically absent.[9, 10] The enlarged cardiac shadow on x-ray and the abnormal electrocardiographic changes characteristically return to normal after the administration of thiamine. Usually clinical improvement occurs much more rapidly than disappearance of the electrocardiographic abnormalities; in advanced cases these abnormalities and cardiac enlargement may persist indefinitely.

Clinical evidences of vitamin deficiency are usual but not invariable. It has been emphasized that severe polyneuritis is present only in the milder cases of congestive failure because the presence of such neuritis interferes with locomotion and work and thus protects the heart. Anesthesias and paresthesias of the extremities, chelosis, decreased or absent knee jerks, painful glossitis, anemia, hyperkeratinized skin lesions, and hypoproteinemia have all been described as evidence of thiamine and associated vitamin deficiencies.

Pathology

Pathologically the heart in cardiac beriberi is most often hypertrophied and dilated, with involvement of both the right and left chambers. Gould[20] describes the heart as globular with marked dilatation particularly of the right ventricle. In adults the heart frequently weighs 500 to 600 Gm. Microscopically edema and hydropic degeneration occur, particularly of the subendocardial muscle fibers and the conduction bundle, together with marked edema of the interstitial connective tissues.[5] Dock stated that mural thrombi are often attached to the trabeculae carneae of the ventricles.[13] No evidence of inflammation is found. Weiss[4] emphasized that the observed histologic changes are neither specific nor characteristic and can be found in other diseases.

Diagnosis

When the classical hyperkinetic syndrome associated with predominantly right-sided failure occurs in beriberi heart disease, the diagnosis is not difficult. With bilateral failure and in the absence of a rapid circulation, as so often occurs in the Occidental variety, the clinical manifestations may be quite similar to other forms of heart failure. Of great importance is the history of dietary thiamine deficiency. In America the vast majority of cases are chronic alcoholics, predominantly males; a few occur in diet faddists and in patients with gastrointestinal disorders. The absence of other etiologic factors increases the possibility of cardiovascular beriberi. Other signs of vitamin deficiency usually are present. Finally, of great diagnostic significance is the favorable therapeutic response to thiamine administration.

Mention has been made of the coexistence of beriberi with other organic types of heart disease. In a patient with heart failure of known etiology, particularly when there is a history or evidence of an inadequate diet, when signs and symptoms of failure fail to respond to the usual therapeutic regime, an additional factor of thiamine deficiency should be strongly considered.

Therapy

Specific therapy for beriberi heart disease consists in the administration of thiamine chloride. Milder cases require 10 to 30 mg. 3 times a day, whereas the more severe cases may require 100 mg. thrice daily. Intravenous or subcutaneous administration should be used when associated gastrointestinal or liver disorders may interfere with the absorption of thiamine. In markedly edematous or severely dyspneic patients digitalis, oxygen, salt restriction, and diuretics should be used. As Blankenhorn and co-workers[9] have pointed out, there is considerable doubt regarding the dictum that digitalis is without value and that if the heart responds well to this drug the diagnosis of beriberi is eliminated. In the acutely ill patient, therapy should be immediate and no time should be lost with diagnostic studies or test thiamine-deficient diets, since some patients may rapidly develop terminal shock.

Report of Cases

Case 1. W. B., a 51-year-old white man was admitted to the hospital on November 17, 1953. He complained chiefly of shortness of breath, weakness, and swelling of the ankles, associated with a severe nocturnal cough and sense of substernal congestion. These complaints were of 6 months' duration but had markedly increased in the month prior to admission.

The patient had consumed large quantities of alcohol, chiefly in the form of beer. A grossly deficient dietary history was also elicited. He was a rural mail carrier and stated that he rarely ate during the day and at night was fatigued but readily revived himself with 6 to 8 bottles of beer, which with several drinks of whisky constituted his main caloric intake. There was no past history of rheumatic fever, high blood pressure, serious illnesses, or any known cardiac disorder.

Physical examination revealed a worn but not emaciated, dyspneic, ruddy, chronically ill-appearing man. The blood pressure was 100/80, the pulse 92, the temperature 98.6 F., and the respirations were 20 per minute. The weight was 139 pounds. There were fissures in the corners of the mouth. The neck veins were distended. Examination of the lungs was negative. The second pulmonic sound was accentuated, and the cardiac tones were of poor quality. The rhythm was regular. There was a distinct, moderately loud, low-pitched, apical systolic murmur. The liver was

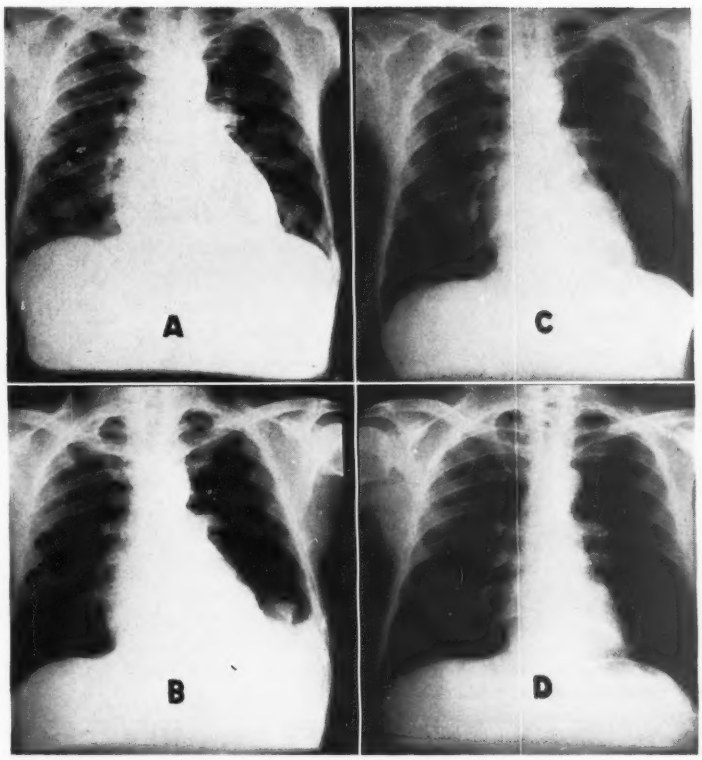


FIG. 1. Case 1. Serial roentgenograms showing decrease in cardiac size and diminished pulmonary congestion following administration of thiamine chloride. *A*. November 18, 1953, admission film prior to administration of thiamine chloride. *B*. November 23, 1953, 4 days after thiamine administration. *C*. December 1, 1953, discharged from hospital. *D*. February 4, 1954, patient ambulatory.

felt 2 fingerbreadths below the costal border, and there was moderate pitting edema of the extremities. The reflexes were active.

Laboratory studies revealed a red-cell count of 3.9 million, 10 Gm. per cent of hemoglobin, and a white-cell count of 7,300, with a normal differential count. The urine was normal except for a trace of albumin. The serum protein was 6.75 gm. per cent, the alkaline phosphatase was 2.3 units, and the cephalin flocculation test was 2+. Urobilinogen in the urine was not increased. Repeated examinations of the sputum for acid-fast bacilli were negative. A bromsulphalein test showed dye retention of 13.2 per cent. A Wassermann test was weakly positive. The spinal fluid examination was normal.

An x-ray of the chest (fig. 1*A*) revealed gross diffuse cardiac enlargement with pulmonary congestion and some fluid in the left base. An electrocardiogram showed low T waves (fig. 2). The venous pressure on November 19, 1953, was 195 mm. of water, and the circulation time was 24 seconds.

The diagnosis of cardiovascular beriberi was made and the patient was kept at bed rest, placed on a high-carbohydrate, high-protein diet, and was given 200 mg. of thiamine chloride subcutaneously 3 times a day.

The patient's response was slow but definite. He lost weight, edema disappeared, and there was relief of dyspnea and cough. The urinary output was very satisfactory, and on November 23, 1953, 4 days after the administration of thiamine, the heart had decreased somewhat in size and there was diminished pulmonary congestion (fig. 1*B*). On November 27, 1953, the heart was still large and globular, but fluoroscopic examination failed to show any left atrial enlargement and the pattern was not consistent with pericardial effusion.

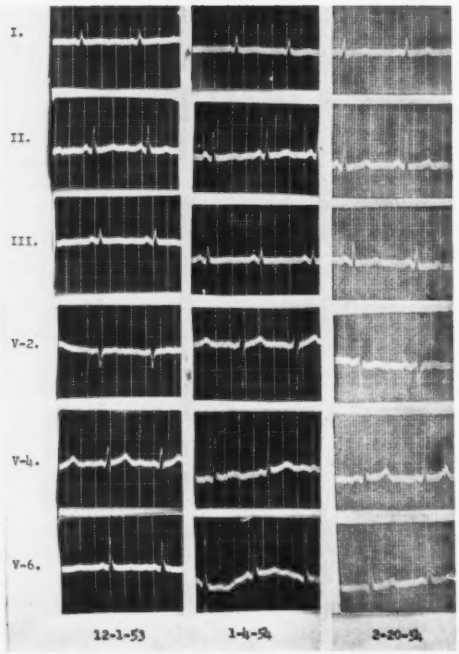


FIG. 2. Case 1. Electrocardiograms demonstrating the response to thiamine chloride in beriberi heart disease. Note flattened T waves on December 1, 1953, before thiamine therapy, as compared with the tracing on February 20, 1954, following the clinical response to vitamin B_1.

On December 1, 1953, after the patient had been maintained on the same therapy, the heart had decreased considerably in size, although there was still some enlargement, and all pulmonary congestion had disappeared (fig. 1*C*). The patient had lost a total of 14 pounds. The liver, though still palpable, was much smaller and ascites was not evident. The patient looked and felt much better, was allowed up from his bed, and was discharged on December 3, 1953, to his home with thiamine chloride, 50 mg. to be taken 3 times daily by mouth.

The patient showed progressive improvement at an office visit on January 4, 1954. He had continued his diet, rest, and thiamine at home. There was no edema, although the electrocardiographic and roentgenologic studies were unchanged. On February 4, 1954, the patient showed continued improvement clinically and an x-ray of the chest showed the heart size to be perfectly normal (fig. 1*D*). The electrocardiogram, however, still showed the original abnormalities. On February 20, 1954, the patient was still feeling very well; there was no dyspnea or cough, and while not back at work, he was much more active. Examination revealed no edema, the liver was barely palpable, and the heart examination revealed normal tones but no murmurs. The electrocardiogram (fig. 2) showed marked improvement and was considered normal. He was advised to continue taking brewer's yeast for several months and was cautioned against poor dietary habits and alcoholic consumption.

This case has been presented as an instance of Occidental beriberi heart disease. Important diagnostic factors were the easily elicited history of dietary deficiency, the signs and symptoms of heart failure, and the excellent clinical response to thiamine chloride. It is true that, aside from cheilosis, general appearance, and anemia, there was no other evidence of vitamin deficiency, but as has been pointed out, this is often the case. Characteristically, the enlarged heart and the abnormal electrocardiogram returned to normal some time after the relief of the symptoms of congestion.

As has been shown, the original concept of beriberi heart disease has been considerably modified and broadened. In the Occident particular emphasis should be placed on the signs and symptoms of congestive failure in a patient on a known vitamin B-deficient diet, with demonstrable improvement after thiamine chloride therapy. The case presented illustrates many of the present concepts of beriberi heart disease and emphasizes that a more liberal diagnostic approach on this subject will undoubtedly permit one to identify and to treat successfully more patients with this condition.

Case 2. E. B., a 48-year-old white man was admitted to the hospital on March 31, 1955.

His main complaints were dyspnea and ankle edema of 3 weeks' duration. He had had chorea at the age of 10. There had been no known rheumatic fever. At the age of 15 the patient had been told he had a "heart condition." Fifteen years before admission the patient had been told he had "high blood pressure" and subsequently it was "as high as 210" and caused his rejection by the Army. Ten years before admission the patient developed rheumatoid arthritis, which so limited his activities that for several years he could scarcely walk alone and could only shuffle about the house. The patient admitted to a grossly deficient diet and stated that he had eaten only

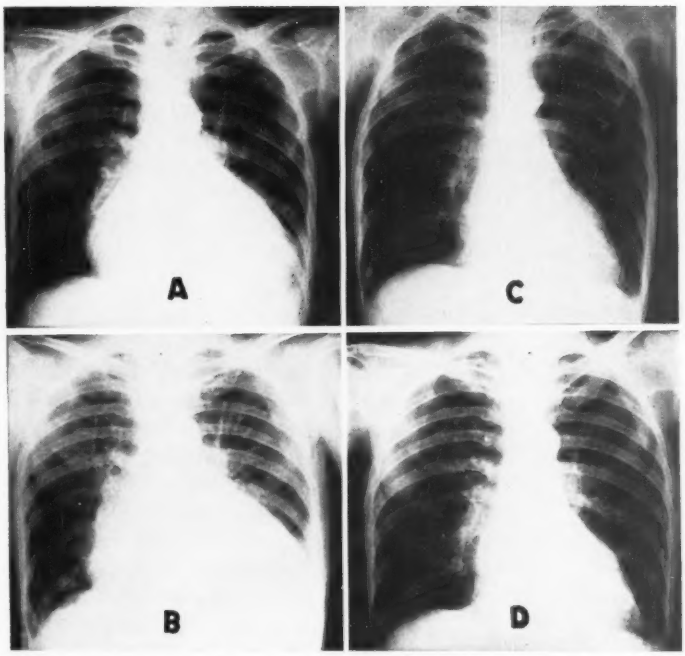


FIG. 3. Serial roentgenograms in case 2. *A*. March 31, 1955, on admission prior to administration of digitalis or thiamine chloride. *B*. April 4, 1955, following administration of digitalis and diuretics but no thiamine, shows progressive cardiac enlargement and pulmonary edema. *C*. April 12, 1955, diminution in cardiac size and pulmonary edema following addition of thiamine chloride to therapeutic regime. *D*. April 18, 1955, continued improvement at discharge.

meal a day for the preceding 10 years. Previous records revealed that the patient had been hospitalized in July 1954 with severe epistaxis and that the blood pressure was recorded as 170/104 mm. Hg.

Approximately 3 weeks before admission, the patient first noted slight ankle edema followed by increasing shortness of breath on exertion. One week prior to admission the patient developed orthopnea. He had been given some unknown diuretics, without benefit, but no digitalis. Because of the increasing severity of these symptoms, the patient was sent to the hospital.

Physical examination revealed a pale, dyspneic, acutely and chronically ill-appearing man. The blood pressure was 190/120, pulse 98, respirations 20, temperature 97.8 F., and weight 140 pounds. The tongue was red and there were fissures in the corners of the mouth. The eyes appeared puffy. Moist rales were present at both lung bases, although there was no dullness on percussion. The heart was markedly enlarged with forceful apex beat noted in the seventh interspace in the midaxillary line. A loud, rough systolic murmur was heard at the apex, transmitted to the axilla. The second pulmonic sound was accentuated. The liver was felt 2 fingerbreadths below the right costal border. No ascites was noted. The fingers and ankles revealed arthritic deformities and there was extensive pitting edema of the legs and ankles.

Laboratory studies revealed a red-cell count of 4.3 million per mm.^{3}, 13 Gm. per cent of hemoglobin, and a white-cell count of 8,100, with a normal differential count. The blood urea was 50 mg. per cent. The urine was normal, with a specific gravity of 1.025. The serum protein was 6.5 Gm. per cent, with a normal albumin-globulin ratio. A serologic test for syphilis was negative. An electrocardiogram was essentially normal. The circulation time (arm-to-tongue with Decholin) was reported as 15 seconds, and the venous pressure was 140 mm. of water. An x-ray of the chest on admission (fig. 3*A*) revealed marked cardiac enlargement with a globular heart and engorgement of the pulmonary vessels. The patient was considered to have chronic rheumatic endocarditis with mitral insufficiency and congestive heart failure as well as rheumatoid arthritis, essential hypertension, and malnutrition.

TABLE 1.—*Weight Loss in Case 2 Following Addition of Thiamine Chloride*

Date	Weight	Output	Pulse	Digoxin (mg.)	Thiomerin (ml.)	NH_4Cl (Gm.)	Thiamine (mg.)	Aminometradine (mg. 3 times daily)
3-31	140	900	96	—		8		
4-1	139	1500	90	1.0		8		
4-2	140	—	80	1.0	1.5	8		
4-3	144	1800	90	1.0		8		
4-4	146	1800	84	1.0	1.5	8	300	
4-5	145	900	66	2.0		2	300	
4-6	140	2900	66	1.0			400	200
4-7	127	4400	70	1.0			400	200
4-8	120	1450+	60	1.0			400	200
4-9	112	3200	64	1.0			400	200
4-10	109	1800+	64	0.5			300	
4-11	109	1000	64	0.25			200	
4-12	110	1000	64	0.25			100	
4-20	109	—	64	0.25			100	

On the succeeding 6 days the patient was given 6 mg. of digoxin as well as ammonium chloride, 2 Gm. 4 times daily, and 2 injections of a mercurial diuretic. This treatment produced no diuresis; in fact, the patient grew worse as evidenced by a 6-pound gain in weight and increasing heart size and pulmonary congestion (fig. 3*B*).

At this time the possibility of a coexisting thiamine deficiency was considered, and on April 4 the patient was given thiamine chloride, 100 mg. 3 times daily, subcutaneously. On April 6 the thiamine chloride was raised to 100 mg. 4 times daily and aminometradine (Mictine), 200 mg. 3 times daily, was added to the therapeutic regimen.

Diuresis and weight reduction were immediately produced and in the next 6 days the patient lost weight, from 146 to 109 pounds, a total of 37 pounds, as seen in table 1. The pulse slowed, edema vanished, and symptoms of dyspnea and orthopnea disappeared.

An x-ray of the chest on April 9 revealed a marked decrease in the heart size and absence of pulmonary edema. On April 12 there was still further reduction in the cardiac size (fig. 3*C*). The patient was maintained on digoxin, 0.25 mg. daily, and a high-carbohydrate, high-vitamin diet with supplementary thiamine chloride. A final x-ray of the chest on April 18 (fig. 3*D*) revealed still further reduction in the cardiac size. The patient was discharged from the hospital on April 20, 1955, with the above medications and diet.

This case has been presented as an instance of chronic rheumatic endocarditis with congestive failure, complicated by thiamine chloride deficiency. At first the factor of thiamine deficiency was overlooked. However, because of no response to digitalis, ammonium chloride, diet, and mercurial diuretics, vitamin B_1 was added to the therapeutic program with very gratifying results, characterized by diuresis, weight loss, a subsidence of symptoms, and a reduction of cardiac size and pulmonary edema. Although a proprietary drug, aminometradine, was given at approximately the same time, it is hardly conceivable that this drug could have caused such a response when a number of other cardiac drugs had failed to influence the edema or clinical course. Although the therapeutic response to thiamine is moderately slow, several of Blankenhorn's[9] cases responded to parenteral medication very rapidly and dramatically. Undoubtedly in a number of cases of organic heart disesae with congestive heart failure there is a contributing factor of thiamine deficiency, thus in effect constituting a form of beriberi heart disease. Failure to recognize this factor in the management of some cases of organic heart disease with congestive failure will result in an insufficient control of symptoms and an inadequate clinical response.

CONCLUSIONS

An outline of the development of the current concept of beriberi heart disease, particularly as it occurs in the Occident, has been presented.

The etiology, symptomatology, diagnosis, and treatment of this condition have been described.

Two cases of Occidental beriberi heart disease with a typical therapeutic response to thiamine chloride have been presented.

It has been emphasized that some patients with known organic heart disease in congestive failure may have a coexisting factor of thiamine chloride deficiency that will influence the clinical manifestation of failure and necessitate supplementary vitamin B_1 therapy.

Classical beriberi heart disease as originally described in the Orient was graphically por

ayed as predominantly right-sided heart ilure in the face of a hyperkinetic circula- on. In the Occident, and particularly in merica, many cases of beriberi heart disease not conform to this dramatic syndrome. A oader diagnostic concept has permitted the cognition and treatment of an increasing mber of patients with beriberi heart dis- se who respond to thiamine after having en refractory to all other measures.

Summario in Interlingua

Es delineate le disceloppamento del conception currente de beriberi cardiac, specialmente como illo occurre in le Occidente.

Es describite le etiologia, symptomatologia, diagnose, e tractamento de iste condition.

Es presentate 2 casos de beriberi cardiac occidental, con un typic responsa therapeutic a chloruro de thiamina.

Es signalate que certe patientes cognoscitemente con organic morbo cardiac in disfallimento congestive ha etiam un co-existente carentia de chloruro de thiamina, influentiante le manifestation clinic de disfallimento e rendente necessari un therapia de vitamina B_1 supplementari.

Classic beriberi cardiac, originalmente describite in le Oriente, esseva representate como disfallimento cardiac predominantemente dextero-lateral in le presentia de circulation hypercinetic. In le Occidente, e particularmente in America, multe casos de beriberi cardiac non corresponde a ille tableau dramatic. Un conception diagnostic plus liberal ha permittite le recognition e le tractamento de un crescente numero de patientes con beriebri cardiac qui responde a thiamina post haber essite refractori a omne altere mesuras.

REFERENCES

Aalsmeer, W. C., and Wenckebach, H. F.: Herz und Kreislauf bei der Beri-Beri Krankheit. Wien. Arch. inn. Med. **16**: 193, 1929.[5]

Kepler, E. J.: Beriberi from a diet of raw starch. J.A.M.A. **85**: 409, 1925.

Scott, L. C., and Hermann, G. R.: Beriberi ("Maladie des Jambes") in Louisiana with especial reference to cardiac manifestations. J.A.M.A. **90**: 2083, 1928.

4. Weiss, S., and Wilkins, R. W.: The nature of the cardiovascular disturbance in vitamin deficiency states. Tr. A. Am. Physicians **51**: 341, 1936.[5]
5. —, and —: The nature of the cardiovascular disturbances in nutritional deficiency states. Ann. Int. Med. **11**: 104, 1937.
6. Blankenhorn, M. A.: The diagnosis of beriberi heart disease. Ann. Int. Med. **23**: 398, 1945.
7. Keefer, C. S.: The beriberi heart. Arch. Int. Med. **45**: 1, 1930.
8. Goodhart, R., and Jolliffe, N.: Role of nutritional deficiencies in production of cardiovascular disturbances in alcohol addicts. Am. Heart J. **16**: 569, 1938.
9. Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Rustin, R. S.: Occidental beriberi heart disease. J.A.M.A. **131**: 717, 1946.
10. Benchimol, A. B., and Schlesinger, P.: Beriberi heart disease. Am. Heart J. **46**: 245, 1953.
11. Alleman, R. J., and Stollerman, G. H.: The course of beriberi heart disease in American prisoners of war in Japan. Ann. Int. Med. **28**: 949, 1948.
12. Vilter, C. F.: Beriberi heart disease at the Cincinnati General Hospital. Cincinnati J. Med. **26**: 153, 1945.
13. Dock, W.: Marked cardiac hypertrophy and mural thrombosis in beriberi heart. Tr. A. Am. Physicians **55**: 61, 1940.
14. Hussey, H. H., and Katz, S.: Beriberi heart disease and pulmonary embolism. Report of three cases. M. Ann. District of Columbia **11**: 247, 1942.
15. Swank, R. L., Porter, R. R., and Yeomans, A.: Production and study of cardiac failure in thiamine deficient dogs. Am. Heart J. **22**: 154, 1941.
16. Williams, R. D., Mason, H. L., Powers, H. M., and Wilder, R. M.: Induced thiamine (vitamin B_1) deficiency in man. Relation of depletion of thiamine to development of biochemical defect and of polyneuropathy. Arch. Int. Med. **71**: 38, 1943.
17. Cowgill, G. R.: Vitamin B, clinical aspects. Internat. Clinic **4**: 54, 1934.
18. Weiss, S.: Occidental beriberi with cardiovascular manifestations: Its relation to thiamine deficiency. J.A.M.A. **115**: 832, 1940.
19. Hashimoto, H.: Acute pernicious form of beriberi and its treatment by intravenous administration of vitamin B_1 with special reference to electrocardiographic changes. Am. Heart J. **13**: 581, 1937.
20. Gould, S. E.: Pathology of the heart. Springfield, Ill., Charles C Thomas, 1953, p. 520.

CLINICAL CONFERENCE

Editor: EDGAR V. ALLEN, M.D.
Associate Editor: RAYMOND D. PRUITT, M.D.

Hyponatremia

By JACK ORLOFF, M.D., MACKENZIE WALSER, M.D.,
THOMAS J. KENNEDY, JR., M.D., AND FREDERIC C. BARTTER, M.D.

DR. JACK ORLOFF: The conference this afternoon is concerned with an analysis of the significance and pathogenesis of hyponatremia, the clinical state associated with a lowered concentration of sodium in the plasma. This has been a particularly confusing subject for a number of years, and unless one is clearly aware of the physiologic significance of this derangement, the response to therapy may be an unwarranted surprise.

There are many clinical situations in which hyponatremia occurs. We have selected a few interesting examples of the syndrome that will be discussed in some detail. Before introducing the speakers, I should like to summarize some of our current views concerning hyponatremia.

Perhaps the main source of confusion regarding this syndrome has been the lack of appreciation of the basic fact that the concentration of sodium in the extracellular fluid is largely determined by the relationship between the intake and excretion of water, rather than by the relationship between the intake and output of salt. The reason for this is that sodium occupies a unique position in the body. It, together with its anions, makes up 90 per cent or more of the osmotically active constituents of the extracellular fluid. Consequently the concentration of sodium in plasma and extracellular fluid reflects the effective osmotic pressure* of the extracellular fluid and provides no information concerning the total amount of sodium in the body. Furthermore, since the intracellular space is in osmotic equilibrium with plasma and interstitial fluid, the concentration of sodium is a measure of the effective osmotic pressure of all body compartments.

It should be clear, then, that a low plasma sodium (hyponatremia) is indicative of a lowered effective osmotic pressure of body fluids, with 2 important clinical exceptions. It does not indicate that the sodium content of body fluids is decreased, although hyponatremia and sodium depletion may occur together; most often hyponatremia is observed in edematous patients in whom total body sodium may be markedly increased. Hyperglycemia and hyperlipemia are the important clinical exceptions to the generalization that hyponatremia and hypo-osmolality (a lowered effective osmotic pressure) are synonymous. In the first instance, the addition of a relatively nonpenetrating, osmotically active substance, glucose, to the extracellular fluid increases its osmotic pressure and effects a redistribution of body fluids. Water is with-

Presented by the Staff of the National Heart Institute at the Combined Clinical Staff Conference of the National Institutes of Health, Bethesda, Md., October 10, 1957. Dr. Mackenzie Walser, formerly with the Institutes, is now with Johns Hopkins Hospital.

*Effective osmotic pressure is that exerted by solutes that do not penetrate cell membranes rapidly. Urea may contribute appreciably to total osmotic pressure. However, it does not affect the distribution of water between cells and surrounding fluids, since it penetrates cells freely and its concentration in cell water and extracellular fluid water is approximately equal.

drawn from cells until a new equilibrium is reached, diluting the sodium in the extracellular fluid in the process. In this situation the extracellular fluid volume is expanded, the intracellular volume is diminished, and the concentration of sodium is decreased, but the effective osmotic pressure may be normal or elevated. In the case of hyperlipemia, the situation is altered in another fashion. The large lipid molecules increase the solid content of a unit of plasma and thereby diminish the water content. Consequently the concentration of sodium in 1 ml. of plasma is decreased, whereas the concentration of sodium in 1 ml. of plasma water is normal, as is the effective osmotic pressure.

The important point to recognize at this juncture is that exclusive of hyperglycemia and hyperlipemia, the finding of a lowered concentration of sodium in plasma is always indicative of dilution, the relative retention of water in excess of solute in the body. The common denominator in all cases of hyponatremia must then be an inability to excrete ingested water with sufficient rapidity to maintain a normal osmotic pressure. The one possible, though unproved, exception to this generalization will be mentioned later.

The regulation of water balance in man is complex, and the numerous factors involved provide opportunities for a large variety of abnormalities, any one of which may lead to an impairment of water excretion and resultant hypo-osmolality. In order to define the numerous defects in regulation that theoretically can produce hypo-osmolality, I should like to review briefly the physiology of water balance.

As you all know, the main routes of water loss are the skin, lungs, gastrointestinal tract, and kidneys. We may dispense with the first three by stating that irrespective of the precipitating factor, the kidney is ultimately responsible for the maintenance of hyponatremia. It is this organ together with the pituitary that serves as the major regulator of water balance.

In normal man approximately 20 per cent of the plasma perfusing the kidneys is filtered at the glomeruli. The ultrafiltrate so formed is delivered to the proximal segment, where it is reduced in volume. Eighty to 85 per cent of the tubular fluid is reabsorbed in this area. Urine remaining in the tubule is isosmotic, i.e., has the same osmotic pressure as the parent filtrate. Presumably, sodium and anion are reabsorbed actively and water diffuses out passively along the resultant osmotic gradient. Residual isosmotic urine is delivered to the loop of Henle and the distal convoluted tubule.* Here most of the remaining sodium and anion are reabsorbed. The membrane in the distal convoluted tubule has a peculiar property; it is freely permeable to water only when antidiuretic hormone (ADH) is present. In the absence of ADH, the membrane is relatively impermeable to water so that, despite the osmotic gradient established by the removal of electrolyte in the distal segment, most of the water remains within the tubular lumen, and the urine thereby becomes dilute (hypotonic to plasma). Water remaining within the tubule after electrolyte abstraction has been termed solute-free water, which means water released for excretion (freed, as it were) by abstraction of solute (sodium and anion) from isosmotic urine. Theoretically, approximately 20 liters a day of water could be excreted by adult man in the total absence of ADH, if no other factors were involved and if virtually all the remaining sodium were removed in the distal segment. However, this is an oversimplification and some water probably diffuses out in both the distal convoluted tubule and the collecting duct, even in the absence of ADH.

In the presence of ADH, the sequence of events changes. Under these circumstances a hypertonic urine may be excreted, so that water may be retained in excess of sodium promoting the development of dilution hyponatremia. ADH is thought to increase the permeability of the distal convoluted tubule to water, so that for all intents and purposes, when ADH is present, this area of the tubule functions as does the proximal segment. Al-

*For purposes of discussion the loops of Henle will be considered as included in the distal segment.

though electrolyte is again abstracted in the loop of Henle and distal convoluted tubule, freeing water in the process, water may now diffuse out of the distal convoluted segment until osmotic equilibrium is achieved. A small volume of residual isosmotic urine containing the nonreabsorbed solutes is delivered to the collecting duct* where once again water without solute is removed. The resultant hypertonic urine is excreted.

In view of these facts it is evident that there are a number of possible disturbances in the renal regulation of water excretion that may contribute to the development of dilution hyponatremia. Perhaps the simplest way to view this, as well as to provide a basis for a classification of hyponatremia, is to list the requirements for the rapid excretion of water in excess of solute, since in the final analysis this is the only device the body has to prevent the development of hyponatremia.

The ability to form a dilute urine and to excrete water with sufficient speed to maintain a normal osmotic pressure in the face of large intakes of fluid depends upon (1) the filtration rate, (2) volume flow to the loops of Henle and the distal convoluted tubule, (3) the reabsorption of sodium and anion in this area with resultant freeing of water, and (4) the permeability of the tubule membrane to water in the diluting area. This last is a function of an intact hypothalamico-hypophyseal system. I should like to propose that most, if not all, cases of dilution hyponatremia may be considered as being the result of a disturbance in 1 or more of these 4 factors.

The first disturbance to be considered is inadequacy of filtration. This is an obvious cause of hypo-osmolality. It is certainly the situation in hyponatremia seen in a nephrectomized animal and in an anuric patient, and is at least a contributory factor in patients with renal insufficiency in whom the number of functioning nephrons is reduced. In the latter group, when filtration rate is seriously depressed and insufficient urine is delivered to the diluting site, the relatively small volume of urine that can be excreted (even if this area of the kidney were operating normally) may be insufficient to overcome dilution produced by the administration of intravenous fluids. In some instances, hyponatremia may develop on what otherwise would be considered a normal fluid intake. Admittedly an added factor in these patients may well be persistent ADH secretion. Even in normal man it is possible, though certainly rare, to overwhelm the filtering capacity of the kidney and produce water intoxication. On the other hand and this is not an uncommon occurrence, if loss of extracellular fluid through vomiting diarrhea, excessive sweating, or shock compromises glomerular filtration, water administered in order to replace volume losses may not be excreted rapidly enough to prevent hyponatremia. In contrast to other cases of hypoosmolality, these may be associated with true sodium depletion. Dilution hyponatremia following salt depletion conceivably could occur even though a dilute urine were being excreted. More often the secretion of ADH, and resultant urine hypertonicity, is an important contributory factor. Dr. Walser will discuss this aspect of the problem in greater detail.

Dilution hyponatremia may also occur as a result of a reduction in volume flow to the diluting segment, not necessarily secondary to a decrease in the number of functioning nephrons. Clearly, if for some reason little or no sodium were delivered to the distal segment, it would be impossible to produce sufficient sodium-free water to prevent the development of bodily dilution. This may be the situation in some edematous patients in whom the reabsorption of sodium and anion may be virtually complete in the proximal segment. Under these circumstances excreted urine may be persistently hypertonic. A full description of this abnormality will be presented by Dr. Kennedy.

A third disturbance that may interfere with urinary dilution and provide the basis for hyponatremia is a reduction in the capacity of the distal segment to reabsorb sodium and thereby to free water. This may be a significant

*ADH may also increase the permeability of this area to water.

factor in adrenal insufficiency as well as in those cases of chronic nephritis associated with increased rates of salt excretion. In both, the sodium reabsorptive capacity of the distal segment is decreased despite adequate flow to this area, and consequently solute-free water may not be formed in large amounts. Both these clinical situations may also be complicated by an associated fall in extracellular fluid volume and filtration rate. Whether persistent secretion of ADH may also be an important factor, as many have suggested, is not certain. In contrast to edematous patients with lowered osmotic pressure, dilution hyponatremia in adrenal insufficiency and in so-called "salt-losing nephritis" occurs in association with true salt depletion; thus both the concentration and total body content of sodium are decreased.

I should like to comment more fully on the role of ADH in the development of hyponatremia. As we have already noted, an important requirement for the excretion of water is that the membrane in the distal tubule remains relatively impermeable to water, which it does only when ADH secretion is in abeyance.

The importance of the hypothalamico-hypophyseal system insofar as it affects urine flow is well known. Normally, a rise in effective osmotic pressure of the extracellular fluid stimulates osmoreceptors in the anterior hypothalamus to effect the discharge of ADH from the hypothalamus and the posterior pituitary. The latter gland apparently serves as a storage depot for the hormone. As already stated, ADH increases the permeability of the distal segment to water and promotes both a decrease in urine flow and the elaboration of a hypertonic urine. Hypo-osmolality of the extracellular fluid normally causes the osmoreceptors to interfere with the secretion of ADH, and water diuresis ensues as a result of a decrease in water permeability of the distal segment. The nature of the stimulus to the osmoreceptors that induces ADH secretion is most reasonably viewed as a shrinkage of the pertinent cells due to withdrawal of water by the hypertonic extracellular fluid. Swelling of the cells presumably interferes with the neurosecretory discharge. Consequently in the presence of normal kidney function, unless nonosmotic stimuli are capable of promoting hormone secretion, this regulatory device should always function to prevent the development of hyponatremia. Unfortunately many other stimuli are known to promote the secretion of ADH even when the effective osmotic pressure is diminished and the osmoreceptor presumably is "informed" that no ADH should be secreted. Thus pain, analgesics, barbiturates, morphine, acetylecholine, operative procedures, to name only a few, stimulate ADH secretion. It should not be surprising, then, that so-called "inappropriate" or nonosmotic stimulation of ADH secretion may be an important contributory factor in many cases of hyponatremia. This, together with the enthusiastic administration of excessive volumes of 5 per cent dextrose, is undoubtedly a "pathogenic" factor in many cases of postoperative hyponatremia. Both Drs. Walser and Bartter will discuss in greater detail the role of ADH in the pathogenesis of other types of hyponatremia.

One other possible physiologic alteration that may be of importance in the development of dilution hyponatremia should be considered. It is entirely conceivable, and Dr. Walser will present some evidence favoring the view, that the osmoreceptors or the osmostats, if you will, may be reset at a lower level of osmotic pressure. In essence, this means that a plasma sodium of 125 mEq./L. in a particular subject is "normal" for that individual, and that both the renal capabilities insofar as dilution is concerned and the activity of the hypothalamico-hypophyseal system are undisturbed. This is an exception to the generalization that all cases of dilution hyponatremia should exhibit impaired ability to excrete water. Presumably resetting of the osmostat could occur if a primary decrease in intracellular osmotic pressure were produced either by actual loss of intracellular solute or a change in the osmotic activity of cell contents, so-called "osmotic inactivation" of cell base. If this fall in intracellular osmotic

pressure should occur, the following sequence would prevail. Water would diffuse out of cells in response to the relative hypertonicity of the extracellular fluid. The osmoreceptors would shrink, stimulating ADH secretion. This would result in the retention of ingested water, greater dilution of the extracellular fluid, and a further fall in extracellular effective osmotic pressure. Water will now reenter tissue cells in general, including the osmoreceptors. Once the size of the latter returns to normal (albeit at a lower osmotic pressure) secretion of ADH will cease. At this point a new equilibrium will have been achieved; the osmotic pressure of the fluid compartments will be stabilized at a new but lower level. Although chronic expansion of the extracellular fluid compartment has resulted, intracellular and osmoreceptor volumes are normal. The pituitary system should operate exactly as in the nonhyponatremic individual, responding to rises and falls in effective osmotic pressure, although at a lower level than in a normal individual.

Inactivation of cell base, or resetting of the "osmostat," has been suggested in order to account for chronic, therapeutically unresponsive hyponatremia in certain cardiac and cirrhotic patients, in carcinomatosis, and in so-called "pulmonary salt-wasting syndromes."[1] The latter will be discussed from a different point of view by Dr. Bartter.

In summary, hyponatremia when associated with a lowered effective osmotic pressure of the fluid compartments is, with one possible exception, a consequence of a diminished ability to excrete water. At least 4 major disturbances may account for this abnormality: a lowered filtration rate, diminished volume flow to the diluting segment, a defective sodium transport system, and persistent "inappropriate" secretion of ADH. Theoretically, hyponatremia may also occur if for some reason the osmotic pressure of cells and osmoreceptors diminishes as a result of solute loss or inactivation of cell cation. Finally, it is important to recognize that though hypoosmolality may occur in association with sodium depletion, most often it is observed when the sodium content of the body is increased, as in edematous subjects.

I should not like to leave the impression that each case of hyponatremia may be analyzed from the point of view of a single defect. Many cases are undoubtedly the result of a number of factors that combine to interfere with normal water excretion.

The remainder of the conference will be devoted to an analysis of specific examples of the syndrome of hyponatremia. A broad spectrum of clinical situations is included in this syndrome, and at times the speakers may seem to be contradicting each other. Individual cardiac patients with hyponatremia, for example, may differ insofar as the pathogenesis of the fall in osmotic pressure is concerned.

I should like to introduce Dr. Mackenzie Walser, who was formerly associated with our laboratory and is now a member of the Department of Pharmacology and Medicine at Johns Hopkins Medical School. Dr. Walser will discuss some aspects of the mechanisms of the development of hyponatremia and the therapy employed in edematous subjects with this syndrome.

DR. MACKENZIE WALSER: The role of ADH in hyponatremia is difficult to assess because, unfortunately, there is no reliable method for measuring the rate of production of ADH, nor its concentration in body fluids. Leaf and Mamby[2] and others have determined the amount of antidiuretic materials in the urine of patients with hyponatremia and edema. This is done by injection of aliquots of urine into a water-loaded test animal and measuring the change produced in urine flow. In general, these experiments have supported the thesis that hyponatremia is due to overproduction of ADH. However, there is no reliable evidence that the antidiuretic substances in the urine are identical with ADH, nor that they are the substances responsible for the antidiuresis seen in the hyponatremic subject.

Another approach has been to administer alcohol to patients with hyponatremia by mouth or by vein, in the hope of suppressing the secretion of antidiuretic hormone. It is known that alcohol has this effect in norma

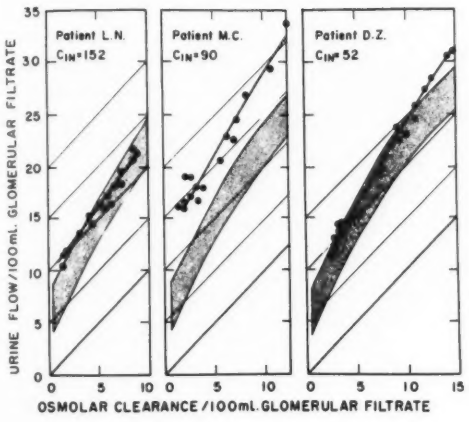


FIG. 1.

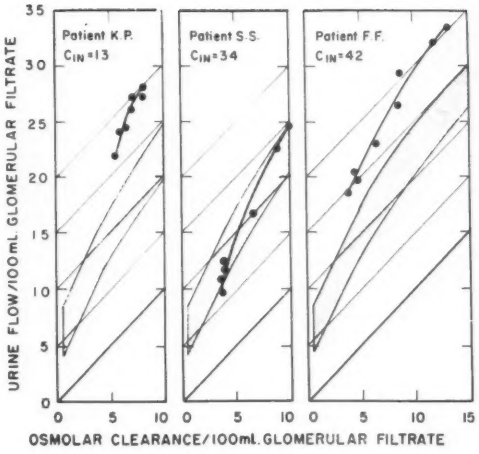


FIG. 2.

subjects. If a water diuresis ensues after giving alcohol, it is good evidence that antidiuretic hormone was being secreted before the alcohol was given. Murdaugh[3] reported that alcohol was successful in producing a water diuresis in a number of patients with postoperative water retention, and in at least 1 patient with hyponatremia and edema on a cardiac basis. On the other hand, Lamdin and associates[4] were unable to produce a water diuresis in several patients with hyponatremia and edema by giving alcohol. This approach is also subject to some uncertainties since alcohol does not always inhibit ADH secretion. Therefore, a positive response in this type of experiment is more significant than a negative one.

A third method of assessing the role of ADH in hyponatremia is to try to exclude some of the other causes of impaired water diuresis. One possible cause is renal dysfunction. In the course of some studies of the diluting function in the nephrotic syndrome we have made some observations on patients who did not have hyponatremia. These are, nevertheless, relevant to the pathogenesis of hyponatremia because patients with hyponatremia and edema very frequently have reduced filtration rates, whether or not they have frank renal disease.

There are at least 3 ways in which renal dysfunction might impair the excretion of water. First, as Dr. Orloff has mentioned, a reduction in the number of functioning nephrons might eventuate in a reduction in the total amount of water that could be excreted, even though the remaining nephrons were diluting normally. Second, salt retention secondary to hypoproteinemia might reduce the amount of sodium salts reaching the distal tubule and impair water diuresis. Third, diseased tubules might lose their ability to dilute. The data to be presented indicate that none of these factors of itself, in the patients studied, can reduce water excretion sufficiently to account for hyponatremia, unless water intake is very great, or unless ADH is present.

Figure 1 shows water excretion plotted as a function of solute excretion in 3 subjects with nephrotic syndrome. In each of these subjects a positive water load of 1 liter or more was produced and maintained continuously, while solute excretion was increased by infusing either isotonic mannitol or acetazoleamide. The shaded area in each graph shows the same relationship as that observed in children with nephrogenic diabetes insipidus, and corresponds approximately to the relationship found in normal subjects. Both urine flow and osmolar clearance are calculated per 100

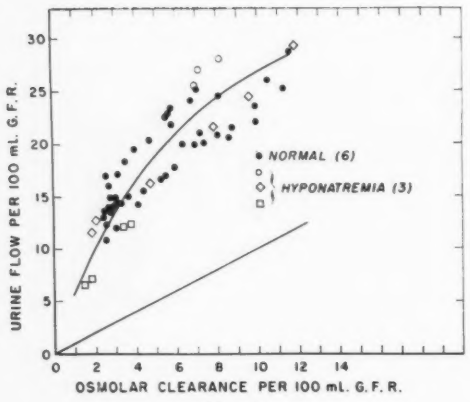


FIG. 3.

ml. of glomerular filtration rate, thus making it possible to compare one subject with another. In this way one obtains an estimate of diluting function per nephron unit, providing of course that filtration rate per nephron remains constant. The heavy lower diagonal line (fig. 1) indicates iso-osmotic urine. In these subjects, 1 of whom had renal insufficiency with a filtration rate of 52 ml. per min., diluting function thus measured was at least as good as normal, as shown by the dots that lie either in or above the shaded area. All these patients had hypoproteinemia and moderate degrees of salt retention. Nevertheless, when ADH secretion was suppressed by administering water, their ability to excrete solute-free water was the same per nephron unit, or more exactly per unit filtration rate, as in normals or better.

Figure 2 shows the results of similar observations in 3 patients with more severe renal insufficiency. Patient K. P. had a filtration rate of 13 ml. per min. and severe chronic nephritis. Nevertheless, diluting function expressed in this way is as good in all 3 patients as in normal subjects. These observations indicate that neither tubular disease of this type nor sodium retention itself need prevent the formation of free water by the remaining functional nephrons.

The question was, can the reduction in the number of functioning nephrons be sufficient to account for hyponatremia even though the remaining nephrons dilute normally? This can be answered by calculating how much solute-free water would be excreted on a 24 hour basis if ADH secretion remained suppressed in these patients. One can calculate from the same data that the rate of solute-free water excretion on a 24 hour basis would be 3 liters for the subject with the lowest filtration rate (patient K. P.). Therefore, to keep serum sodium low in this patient without the aid of ADH, it would be necessary to give 3 liters of water in addition to another liter for insensible loss. Hyponatremia can be produced in any subject by giving enough water, but we are concerned here with persistent hyponatremia in the absence of polydipsia or excessive parenteral loads of water.

These observations in patients with renal disease cast some doubt on the hypothesis that water retention may be the result of either impaired tubular diluting ability in chronic renal disease or the result of salt retention with inadequate quantities of sodium reaching the diluting site in the distal tubule. On the other hand, these data are not relevant to the hypothesis that a fall in filtration rate in a subject with otherwise normal kidneys may account for hyponatremia in the absence of ADH, because the reduced filtration rates seen in these patients are not analogous to the fall in filtration rate that occurs when renal blood flow is reduced. Filtration rate per nephron unit falls when the renal blood flow is reduced in a normal kidney, but the reduction in filtration rate seen in these patients with renal disease is presumably due to a reduction in the number of functioning nephrons.

Therefore, in order to distinguish between the possibility that hyponatremia may be due to a reduction in filtration rate per nephron unit, and the possibility that persistent ADH secretion accounts for hyponatremia, water loads were administered to 6 patients who had low serum sodiums and edema but were excreting concentrated urine. If their hypertonic urines were due to reduced filtration rates per nephron unit, a water load should have little effect on urine concentration since

is known, as shown by Chasis and Smith,[5] hat water loads influence filtration rates to nly a slight extent in human subjects. On he other hand, if ADH were being secreted it ight be possible to inhibit this secretion by a urther reduction in blood osmolality.

Figure 3 shows the results in 3 patients with yponatremia compared to 6 normal subjects. he normal and hyponatremic patients fall ito the same general area. A fourth subject ith hyponatremia (not shown in the figure ecause filtration rate was not measured) also esponded to water loading, with urine osmo- ality falling to 16 mOsm./Kg. Of these 4 atients who responded to water loading, 2 ad congestive heart failure with essentially o sodium in their urine, and the other 2 had he nephrotic syndrome with edema. This bservation provides further support to the hesis that sodium retention does not impair water diuresis when the latter is expressed in this manner. The data from one of these experiments are shown in detail in figure 4. This patient had congestive heart failure thought to be due to myocarditis. His serum sodium was 120 mEq./L. Before the experiment began, his urine concentration (shown as black dots) was higher than his plasma concentration (open circles). After a water load his urine concentration fell to 50 mOsm./Kg. and his urine flow rose. At the point indicated by the right arrow acetazoleamide was injected and a further rise in urine flow occurred. Sodium remained absent from the urine throughout the experiment. The rise in water excretion was associated with a rise in potassium and bicarbonate excretion. This subject's filtration rate was 82 ml. per min. and he had no known renal disease. Two other patients with hyponatremia and edema did not respond to a water load. Both these patients, studied in collaboration with Dr. John Fahey, National Cancer Institute, had neoplastic disease. The occasional failure to observe a water diuresis cannot be cited as evidence for any proposed mechanism of hyponatremia, since such failures may occur occasionally even in normal subjects although they are certainly more common in chronically ill subjects. These failures to observe a water diuresis are presumably due to the continued secretion of ADH conditioned by nonosmotic stimuli, such as pain or discomfort. At present it is impossible to evaluate the role of these other factors in contributing to the production of hyponatremia.

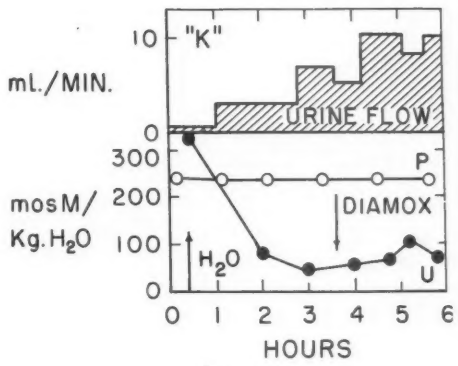


FIG. 4.

The 4 patients who responded normally to water loads seem to fit best into the category of persistent ADH secretion. Since the ADH could be inhibited by a further fall in plasma osmotic pressure, its secretion was evidently being conditioned by osmotic stimuli. Apparently the osmoreceptor center or "osmostat" in these patients has become attuned to an abnormally low level of osmotic pressure. If this is correct, it leaves unanswered the question of how the readjustment of the osmoreceptor center has taken place. One conceivable hypothesis for which there is admittedly no direct evidence is as follows. A number of years ago Baldes and Smirk[6] showed that the level of the osmoreceptor center and the secretion of ADH may be attuned to some function of the volume of the body fluids. These authors administered water load to normal subjects and observed a fall in plasma osmolality. Then these same subjects were depleted of sodium and given another load of water. The depletion of sodium produced a fall of about 12 mOsm./Kg. in the plasma osmotic pressure, which was greater than the fall produced by the water load in the control studies. Nevertheless, at this lower level of osmotic pressure

a response to water loading occurred. The extracellular fluid volume was presumably reduced by the salt restriction and the results suggest, therefore, that the level of the osmoreceptor center was changed.

The converse experiment was also done by giving normal subjects hypertonic salt orally. After 3 hours, when the serum sodium was still high, a water load was given and usually a water diuresis was observed. Apparently, under these circumstances, an elevation in the extracellular fluid volume had raised the level to about that at which the ADH mechanism was operating. In patients with hyponatremia and edema, extracellular fluid volume is obviously increased; yet the setting of the osmoreceptor center is reduced, according to the data presented above. This paradox has been considered at length with respect to sodium retention. Similar considerations may apply to the problem of water regulation. Volume may conceivably be reduced in some critical area.

Finally, I should like to discuss the way we treated these subjects. Water intake was restricted to about a liter a day in every patient. In some cases a 25 to 40 per cent urea solution was given orally, in doses from 50 to 100 Gm. Mannitol was given intravenously as either a 15 or 20 per cent solution in quantities of 1 or 2 liters. These solutes hasten the correction of hyponatremia because they induce a negative water balance, i.e., they require for excretion more water than is given with them. This form of therapy is less effective in the absence of sodium retention because under these conditions the osmotic diuresis sweeps out sodium as well as water. Any number of solutes might be employed for this purpose and it is probably safe to say that almost any solute, which is not metabolized, given without water, will raise the serum sodium. This includes potassium chloride for example. Solutes that are confined to the extracellular space, such as mannitol, lower the serum sodium transiently and then raise it as they are excreted. Unfortunately, the correction of hyponatremia in these patients was not associated with any striking clinical improvement. But they all had severe illnesses and it is difficult to evaluate the role of any single factor in their clinical course. It is worthy of note, however, that none of them complained bitterly of thirst, as do patients who are treated with hypertonic saline.

In summary, the data presented suggest that hyponatremia occurring in these subjects could best be attributed to the continued secretion of ADH, as the result of the osmoreceptor center having become attuned to a lower level of osmotic pressure.

QUESTION: Did you make any gross measurements of renal function—the NPN rise, for example—in patients with renal disease and hyponatremia who were treated by restricting water? Also, how much was water intake restricted?

DR. WALSER: The extent of water restriction depended somewhat on the solute intake. In patients who were getting no salt in their diet or who did not have to have large quantities of parenteral solute, water was restricted to a liter a day. We were able to measure renal function in 2 patients after bringing the serum sodium back up. One was slightly higher and the other was slightly lower.

DR. ORLOFF: Irrespective of the cause of hyponatremia, water restriction obviously will elevate the plasma sodium and plasma osmolality. This in itself cannot be used as an argument concerning the pathogenesis of the lowered serum sodium in a specific case.

QUESTION: Dr. Walser mentioned the possibility of changes in volume effecting a resetting of the "osmostat." Is this an important factor, for instance, in the adrenalectomized patient maintained on cortisone who is subjected to sodium restriction? The original loss is that of extracellular fluid. If this continues, one develops hyponatremia and there is some evidence that this is in relation to ADH secretion. There is nothing obvious to stimulate secretion of ADH except some change in extracellular fluid and plasma volume.

DR. WALSER: Yes, I think that hypothesis makes more sense in the sodium-depleted patients than in the edematous ones.

DR. ORLOFF: In the Addisonian or in anyone whose extracellular fluid volume is seriously depleted, filtration rate also falls appreciably so that it is questionable whether one needs to interpose increased secretion of ADH to account for hyponatremia, although it may be a factor. I do not believe the evidence for increased secretion of ADH is particularly convincing, one way or the other.

QUESTION: Urine osmolality may reach a level of 500 mOsm./L. at a time when glomerular filtration, as measured by creatinine clearances, is perhaps only 70 per cent of the initial value.

DR. ORLOFF: This may be evidence of ADH secretion, although a fall in filtration rate of itself may result in urine hypertonicity in the dog.

Dr. Kennedy will discuss the significance of hyperkalemia and acidosis in patients with edema and hyponatremia. This is an interesting aspect of the problem which, as far as we know, has not been considered in any detail before.

DR. THOMAS J. KENNEDY: Until recently, hyponatremia and hypo-osmolality in patients with congestive heart failure had been interpreted as salt depletion, and hypertonic saline was often administered therapeutically. A not infrequent sequel was catastrophic pulmonary edema. The fact is that salt depletion never co-exists with significant edema; hyponatremia in the edematous patient with heart failure signifies water retention. Recent interest has focused on the mechanism responsible for the dilution of body fluid compartments. I should like to discuss a patient studied at the Clinical Center recently who presented features that have not been emphasized heretofore in the literature. She is typical of a small number of patients who have demonstrated essentially the same condition in either chronic form or acute episodes. It is not known how representative these cases are of the dilution syndrome seen so frequently in congestive heart failure. However, on the basis of the data collected, a tentative formulation of the pathogenesis of the syndrome in this case is advanced, with a few comments on therapy.

The patient was a 29 year old single white woman who was admitted to the Clinical Center in April 1957 for cardiac surgery. The presence of stenosis and insufficiency of aortic, mitral, and tricuspid valves was established, in addition to congestive heart failure, and mitral and tricuspid commissurotomies were performed in early June. One week postoperatively she was found to have hyponatremia, hypo-osmolality, and azotemia while still markedly edematous. Repeated serum electrolyte determinations preoperatively and the blood urea nitrogen had been normal. In addition, the unusual feature in this case, as in 3 others studied, was striking hyperkalemia. Other patients in the group also showed a mild acidosis. We wondered, therefore, whether the whole picture could be put together in terms of a single physiologic dislocation, namely, a severe reduction in the sodium load presented to the distal tubule.

The results of renal function studies are tabulated in table 1. The urine flow was extremely low. Glomerular filtration rate was about 40 per cent of the expected rate, a washout error indubitably contributing to the high value for the inulin clearance seen in the fourth period. The rates of excretion of sodium, potassium, titratable acid, ammonium, and osmotically active solute were all reduced. The urine was concentrated and the free water clearance was negative. After the third period sodium sulfate was administered for the control of hyperkalemia. Since the nephron's reabsorptive capacity for this anion is limited, most of the filtered sulfate remains intraluminal and is excreted together with some cation, which was predominantly potassium in this case. The kaluresis was accompanied by a fall in plasma potassium, which continued beyond the termination of the tabulated study as indicated by the even lower plasma potassium concentration measured 18 hours later. Other effects of the administration of this essentially nonreabsorbable anion are increments in the excretion rates of titratable acid and ammonium, and a sharp decrement in the osmotic pressure of the urine, despite only a modest rise in the osmolar excretion rate.

TABLE 1.—*The Effect of Sodium Sulfate on Water and Electrolyte Excretion and Plasma Composition in a Patient with Hyponatremia and Hyperkalemia*

			Excreted									Plasma		
Time (min.)	V (ml./min.)	GFR* (ml./min.)	Na^+	K^+	T.A.†	NH_4^+	pH	U_{osm} (mOsm./L.)	UV_{osm} (μOsm./min.)	Tc_{H_2O} (ml./min.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	O.P.‡ (mOsm./L.)
			(μEq./min.)										
0	Priming inulin and paraamino hippuric acid. Start sustaining inulin and paraaminohippuric acid at 1 ml./min.												
0											114	6.5	246
54- 72	0.11	29	1	13	6	9	5.3	1108	121	0.39			242
72- 95	0.18	29	1	13	7	9	5.3						242
95-113	0.11	33	1	13	6	9	5.3	1108	123	0.40	114	7.1	242
118	Add to infusion 1050 μOsm./min. sodium sulfate												
138-158	0.44	85	1	44	9	15	4.7	1142	164	0.52			245
158-198	0.47	37	2	81	12	17	4.4	509	241	0.51			245
198-230	0.35	29	6	90	12	13	4.3	699	244	0.62			251
230-259	0.42	22	8	87	10	11	4.2	551	228	0.48	116	5.6	254
260	Discontinue infusion												
1320											120	4.8	248

*GFR = Glomerular filtration rate.
†T.A. = Titratable acid.
‡O.P. = Osmotic pressure.

In these patients the severe reduction in the glomerular filtration rate must effect a very remarkable decrease in the volume of isotonic urine and thus in the absolute amount of sodium chloride reaching that segment of the distal nephron in which urine is diluted by the active transport of sodium chloride. The reduced glomular filtration rate in these cases is secondary to reduced cardiac output and the increased tubular reabsorptive capacity for sodium characteristic of heart failure (secondary hyperaldosteronism). Therefore dilution must be slight, and the subsequent withdrawal of a minimal amount of water in the collecting system could result in the elaboration of a concentrated urine. Sulfate or any other agent that restricts proximal sodium chloride transport should thereby increase the distal load, permit more significant dilution, and result in the excretion of a less concentrated urine. The critical question is, could the reduction in distal sodium load, of the magnitude inferred in this patient, account for the osmotic U/P ratio observed? Relevant data come from observations by Berliner and Davidson.[7] During experiments in which filtration rate was reduced unilaterally by the constriction of a preinstalled renal clamp, they measured the osmotic pressure of the urine in water-loaded dogs in which ADH activity may be assumed to have been in abeyance. At low rates of osmolar excretion and of glomerular filtration, osmolar U/P ratios approaching 2 were encountered. The osmolar U/P ratio seen in this acute experiment was much higher than 2 and possibly requires the assumption of some ADH activity. The procedure was relatively strenuous, and easily could have resulted in stimulation of ADH output. For the greater port of this patient's 80 day balance study, however, osmolar output was very low. It averaged about 100 microosmols per minute or 150 mOsm. per day, and osmolar concentration was not very high, averaging perhaps 600 mOsm./L. with an osmotic U/P ratio of about 2.5.

Here, then, is a clinical situation in which the reduction in filtration rate and osmolar load were greater than the bulk of the observations in water-loaded dogs with one constricted renal artery, and in which the osmolar U/P ratio was only slightly higher than that

achieved in an animal in which we may be certain no ADH activity was operative. When the distal sodium load was increased by diuretics, such as sodium sulfate, mannitol, and mercurials, the urine became dilute as the osmolar load increased. These observations are at least compatible with the idea that the reduced distal sodium load per se is responsible for the hypertonic urine. The possibility remains, however, that the permeability to water of the distal nephron and collecting system has been increased by ADH. If this is true, it is obvious that the ADH release has been triggered either by lower than normal osmolar concentration in body fluid, the reset "osmostat," or by some ill-defined nonosmotic stimulus.

Several features of the long-term course of this patient's illness warrant comment. In these patients, in contrast to those of Dr. Walser, water restriction was not a very practical therapeutic measure. From about the twelfth to thirtieth day of this study, the water intake in all forms except preformed dietary water (estimated to be about 500 ml. per day) was limited to 250 ml. per day. Despite such severe restriction in water intake, the patient failed to lose weight or increase her plasma osmolality; apparently she was able to limit water losses very efficiently.

Another point of interest is that osmotic diuretics, such as mannitol and sulfate, did not result in significant water or weight losses at dosage levels within limits practical for routine clinical application. On the other hand, when mercurial diuretics were administered with aminophylline after preloading with ammonium chloride, they produced a diuresis of sodium and water, a sharp fall in urinary osmotic pressure, and a return toward normal values of plasma sodium and osmotic pressure. Four injections of mercaptomerin effected an 8 Kg. (18.2 per cent) decrease in body weight. Recalling the days when "salt-depleted patients" such as this one were treated with hypertonic saline, note the apparent paradox in which this particular so-called "low salt syndrome" was ameliorated by salt depletion.) Also of interest was the inability to excrete water loads. On approximately the thirty-fifth day, water intake was increased in this patient and was followed by weight gain and further dilution of the serum sodium.

The patterns of potassium excretion in this type of patient are of some interest. For practical purposes it may be assumed that the filtered potassium is completely reabsorbed in the proximal tubule, and that all excreted potassium has been secreted by the cells in the distal segment.[8-10]

Potassium and hydrogen ion in these cells compete for an exchange mechanism that transfers them into the lumen and simultaneously transports sodium out of the lumen. Ordinarily, the capacity of the mechanism is not completely utilized due to an inadequate amount or concentration of counter ion. An increased delivery of sodium to this site, as in electrolyte diuresis, results in an increase in potassium and acid excretion. Conversely, reduction in the load of counter ion by increased proximal sodium reabsorption reduces potassium and acid excretion. The primary effect of mercurial diuretics is to inhibit potassium transport, but the actual change in potassium excretion which follows is conditioned by 2 other factors, the distal sodium load and the capacity of the exchange system. Mercurials are usually employed in situations in which the capacity of the system is increased and in which the load of counter ion is reduced. By inhibition of proximal sodium transport, the diuretic increases the distal sodium load. Thus the ion exchange mechanism, even though inhibited by mercury, may actually secrete more potassium through its uninhibited and previously unused residual capacity. It seemed reasonable to assume that in these patients the capacity of the exchange mechanism was increased as well as underutilized due to the reduced distal sodium load. Potassium and acid retention ensue with hyperkalemia and acidosis.

It was apparent in our studies that manipulations assumed to increase distal sodium load, e.g., administration of sulfate, mannitol, or mercaptomerin promoted the excretion of potassium, ammonium, and titratable acid and

simultaneously lowered plasma potassium. Mercurials appeared to be the most effective; mannitol the least effective. Chlorothiazide (Diuril), a new oral diuretic, caused a small but consistent increment in potassium excretion. It is also evident that only a fraction of this patient's modest daily potassium intake (34 mEq.) appeared in her urine. Fecal measurements were not made. The persistent hyperkalemia probably reflects continuous slight positive potassium balance. The hazard of induction of hypokalemia by therapy should not be minimized as the capacity of the sodium potassium exchange mechanism is undoubtedly supranormal. Plasma potassium levels under 3 mEq./L. were observed in this patient on several occasions following sulfate and mercurial administration. The hazard of hypokalemia also restricts considerably the use of sodium sulfate for its osmotic effect.

In summary, we have presented one of a group of cases seen at the Clinical Center recently in whom water retention occurred in a setting of severe congestive heart failure. All were hyperkalemic and several were acidotic. It is proposed that the hyperkalemia and acidosis reflect renal retention of potassium and hydrogen ion secondary to a distal tubule sodium load sufficiently low to preclude ionic exchange and subsequent excretion of these ions. It is further proposed, tentatively, that water retention and urinary hyperosmolality may be due to the same fundamental defect and need not require, in addition, the invocation of abnormally initiated ADH activity.

DR. ORLOFF: I should like to repeat my earlier statement that at times the speakers may seem to be contradicting each other. Despite the fact that both groups of patients under discussion were edematous, the mechanism of the development of hyponatremia in each differed considerably.

Dr. Frederic C. Bartter will discuss hyponatremia in nonedematous patients with pulmonary disease.

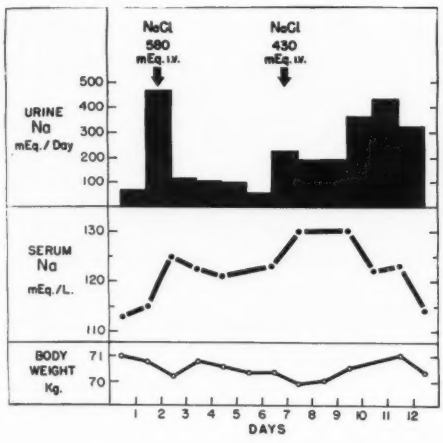
DR. FREDERIC C. BARTTER: First, I should like to describe a syndrome of hyponatremia with continued urinary sodium loss in 2 patients with pulmonary tumors studied recently by Drs. Schwartz, Bennett, Curelop, and me.[11] Then I should like to present our hypothesis, which explains the abnormalities of salt and water metabolism. Finally, I shall try to relate this syndrome to that of hyponatremia in other types of pulmonary disease.

The 2 patients were men with bronchogenic carcinoma. Both developed marked, progressive hyponatremia with continued urinary loss of sodium. There were no symptoms attributable to the salt loss, and no symptoms or signs to suggest dehydration or loss of total body fluid volume at any time. Blood pressure was persistently normal in one and high in the other. In one, "spaces" were determined when the serum sodium was 112 mEq./L. and showed extracellular fluid volume to be substantially *above* normal. In both, fall of serum sodium concentration occurred without change in body weight—and thus in total body water.

Adrenal function was essentially normal in both: 17-hydroxycorticoids were normal and rose normally, as eosinophils fell, with ACTH. Aldosterone excretion was normal. Serum potassium was persistently normal in both, and there were no clinical signs pointing to hypoadrenocorticism.

Renal function, too, was essentially normal in both: urinalyses gave normal results, blood urea nitrogen was never elevated, renal plasma flow was normal, and inulin clearance was normal in one and high in the other. The kidneys were essentially normal on histologic examination. Sodium-retaining steroids produced retention of sodium, loss of potassium, and weight gain in both subjects, showing that they did not have "obligatory" tubular sodium loss.

Salt "loads" in these patients raised the serum sodium only transiently; despite severe hyponatremia, a large proportion of the administered sodium appeared in the urine. This is shown in figure 5, which shows also that weight gain did not occur when the serum sodium was raised in this way. The same phenomenon is shown for the other subject in figure 6.



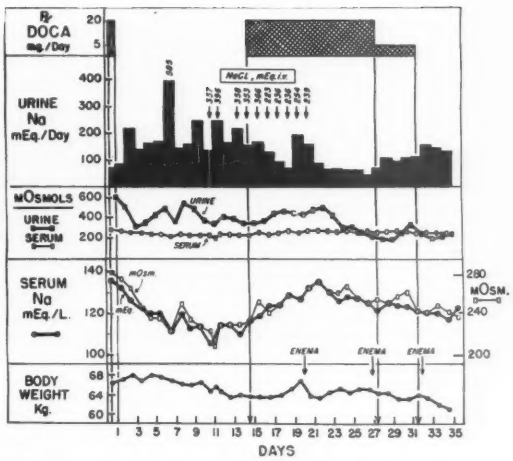


FIG. 5 *Left.* Urine sodium, serum sodium concentration, and body weight during a 12 day balance study of W. F. Dietary sodium intake was as follows: days 1 to 7, 80 mEq.; day 8, 180 mEq.; days 9 to 12, 326 mEq. *(Reprinted by permission from the American Journal of Medicine.*[11]*)*

FIG. 6 *Right.* Urine sodium, urine and serum osmolality, serum sodium concentration, body weight, and steroid therapy during a 35 day balance study of W. A. Dietary sodium intake was as follows: days 1 to 9, 62 mEq.; days 10 to 35, 42 mEq. Supplementary sodium intake is indicated by *arrows. (Reprinted by permission from the American Journal of Medicine.*[11]*)*

The phenomenon that suggested to us the mechanism responsible for the syndrome is also illustrated in figure 6: in both patients the urine was consistently hypertonic to the plasma. In subjects with normal filtration rates, this may be taken as prima facie evidence of the presence of antidiuretic hormone.

When pitressin and water are given to normal subjects,[12, 13] they gain weight and develop hyponatremia with urinary sodium loss. Their urine is, of course, persistently hypertonic to their serum. The urinary sodium loss appears to result both from the increases in glomerular filtration rate they regularly develop and from depression of aldosterone secretion (if initially high) or its failure to rise with sodium loss (if initially low). If water is withheld during the pitressin therapy, however, sodium and water metabolism remain normal.

This brings us to the hypothesis. We postulated that the disease process in these patients leads in some manner to the persistent autonomous and inappropriate secretion of antidiuretic hormone, and that the hyponatremia and sodium loss result from this as they do in normal subjects.

This hypothesis was strengthened by the finding that both subjects could maintain normal sodium and water balance when moderately deprived of water (fig. 7), but promptly developed the full syndrome when additional water was given. Although the hypothesis appeared to fit all the facts, there was no evidence that patients with persistent antidiuretic hormone production would voluntarily drink until the syndrome appeared. We tested this by giving pitressin "blind" to 2 people with normal renal and adrenal function on ad libitum water intakes. They voluntarily drank enough water to develop hyponatremia and maintain it for 2 weeks.

Finally, I should like to consider briefly the possible relation of this syndrome to that of "pulmonary salt loss"[1] and "cerebral salt loss"[14] in general. With the evidence at hand, it is not possible to say that all such cases can or cannot be explained as manifestations of

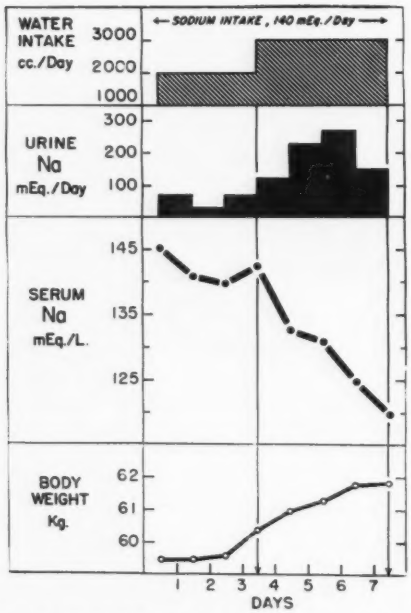


FIG. 7. Fluid intake, urine sodium, serum sodium concentration, and body weight during a 7 day study of W. F. Minimum osmolality of urine (based on $2 \times [Na] + [K]$) ranged from 280 to 440 on days 4 through 7. *(Reprinted by permission from the American Journal of Medicine.*[11]*)*

inappropriate secretion of antidiuretic hormone. Indeed, many of them meet some of the criteria for such an explanation: they have expanded extracellular fluid volumes and lose sodium in the urine as hyponatremia develops. They may differ from our subjects in having a "floor" below which their serum sodium will not fall—a finding that suggests a new "setting" of the osmoreceptor to explain the syndrome. For 2 reasons such a hypothesis appears most unlikely in the case of patients reported here. In the first place, no "floor" could be found in our patients. For example, one was still secreting a concentrated urine containing sodium when his serum sodium had reached 102. In the second place, when the serum osmolality was brought back to a normal level of 280 milliosmolal with desoxycorticosterone, urine tonicity not only did not rise but fell markedly, despite a *decrease* in the total solute in the urine. If osmoreceptors had been "set" for, say, 240, then 280 would represent severe hypertonicity and antidiuretic hormone output should have been maximal, and urine volume minimal, at this time.

The final decision as to whether these 3 groups of patients fall into different, or essentially the same, categories requires further critical data.

DR. ORLOFF: Are there any questions?

QUESTION: Dr. Orloff, in your introduction you predicted that there might be some apparent contradictions in the subsequent talks I wonder if you would describe them and indicate why they are only apparent.

DR. ORLOFF: Although differences of opinion may exist concerning a specific case of hyponatremia, none of the speakers has presented really contradictory evidence regarding the pathogenesis of the syndrome. It should be clear from the discussion that patients with edema and hyponatremia may differ markedly insofar as the basis for the lowering of plasma sodium is concerned. This is also undoubtedly true for nonedematous hyponatremic patients. One has to analyze the individual situation somewhat as I outlined it in my introduction, listing the possible defects that might lead to inadequacy of water excretion. Certainly no one has questioned the primary premise that hypo-osmolality is always secondary to dilution; that is, retention of water in excess of solute.

Dr. Kennedy presented evidence that in the patients he studied, reduction in filtration rate and increased capacity of the proximal segment to reabsorb sodium limited the amount of sodium reaching the diluting segment, thereby providing the basis for inadequacy of water excretion and dilution hyponatremia. He also conceded that increased ADH secretion may have been another factor involved. Dr. Walser argued that reduction in filtration rate per se in certain nephrotics may not be the only cause of hyponatremia, since dilution capacity per unit of glomerular filtration was normal. He postulated that persistent ADH secretion was required to effect hyponatremia in the patients studied. Dr. Bartter argued on the basis of his experimental evidence that

"inappropriate" ADH secretion in 2 patients with pulmonary tumors was the basis for the syndrome of so-called "pulmonary salt-wasting," that is, hyponatremia and natriuresis. This is a very interesting suggestion and in some details is at variance with a hypothesis presented some years ago. At that time it was postulated that a primary decrease in intracellular osmolality, presumably accomplished by inactivation of cell cation, was the essential defect in patients of this nature. Though not clearly stated at that time the sequence of events, if such a defect does exist, might be analogous to that described for resetting of the osmostat. If this were correct, "pulmonary salt wasters" should respond to water loads in a normal fashion, albeit at a lower steady state concentration of plasma sodium. However, the cause of the enhanced salt excretion must be sought elsewhere. It was originally argued that the latter occurrence was a compensatory response to the fall in intracellular osmolality. The arguments against this hypothesis are that gross estimations of water excretion were always abnormal and that in Dr. Bartter's subjects, at least, sodium excretion did not cease on a low salt diet. The latter was not true of the patients studied by Sims et al.[1] and is perhaps indicative of a difference in pathogenesis. More study is necessary to resolve these inconsistencies.

REFERENCES

1. Sims, E. A. H., Welt, L. G., Orloff, J., and Needham, J. W.: Asymptomatic hyponatremia in pulmonary tuberculosis. J. Clin. Invest. **29**: 1545, 1950.
2. Leaf, A., and Mamby, A. R.: The normal antidiuretic mechanism in man and dog; its regulation by extracellular fluid tonicity. J. Clin. Invest. **31**: 54, 1952.
3. Murdaugh, H. V., Jr.: Production of diuresis in hyponatremic edematous states with alcohol. J. Clin. Invest. **35**: 726, 1956.
4. Lamdin, E., Kleeman, C. R., Rubini, M., and Epstein, F. H.: Studies on alcohol diuresis. III. The response to ethyl alcohol in certain disease states characterized by impaired water tolerance. J. Clin. Invest. **35**: 386, 1956.
5. Chasis, H., and Smith, H. W.: The excretion of urea in normal man and in subjects with glomerulonephritis. J. Clin. Invest. **17**: 347, 1938.
6. Baldes, E. J., and Smirk, F. H.: The effect of water drinking, mineral starvation and salt administration on the total osmotic pressure of the blood in man, chiefly in relation to the problems of water absorption and water diuresis. J. Physiol. **82**: 62, 1934.
7. Berliner, R. W., and Davidson, D. G.: Production of hypertonic urine in the absence of pituitary antidiuretic hormone. J. Clin. Invest. **36**: 1416, 1957.
8. —, Kennedy, T. J., Jr., and Hilton, J. G.: Renal mechanisms for excretion of potassium. Am. J. Physiol. **162**: 348, 1950.
9. —, —, and Orloff, J.: Factors affecting the transport of potassium and hydrogen ions by the renal tubules. Arch. internat. pharmacodyn. **97**: 299, 1954.
10. Davidson, D. G., Levinsky, N. G., and Berliner, R. W.: Maintenance of potassium excretion despite glomerular filtration during sodium diuresis. J. Clin. Invest. In press.
11. Schwartz, W. B., Bennett, W., Curelop, S., and Bartter, F. C.: A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am. J. Med. **23**: 529, 1957.
12. Leaf, A., Bartter, F. C., Santos, R. F., and Wong, O.: Evidence in man that urinary electrolyte loss induced by pitressin is a function of water retention. J. Clin. Invest. **32**: 868, 1953.
13. Bartter, F. C., Liddle, G. W., Duncan, L. E., Jr., Barber, J. K., and Delea, C.: The regulation of aldosterone secretion in man: The role of fluid volume. J. Clin. Invest. **35**: 1306, 1956.
14. Cheek, D. B.: Further observations on electrolyte change in tuberculous meningitis: The ratio of the concentrations of bromide in serum and cerebrospinal fluid. Pediatrics **18**: 218, 1956.

ABSTRACTS

Editor: STANFORD WESSLER, M.D.

Abstracters

JONAS BRACHFELD, M.D., Philadelphia
GEORGE B. BROTHERS, M.D., Milwaukee
MASSIMO CALABRESI, M.D., West Haven
IRWIN FREEDBERG, M.D., Boston
HAROLD KARPMAN, M.D., Los Angeles
HERBERT J. KAYDEN, M.D., New York
J. RODERICK KITCHELL, M.D., Philadelphia
SEYMOURE KRAUSE, M.D., Pittsburgh
GEORGE S. KURLAND, M.D., Boston
EUGENE LEPESCHKIN, M.D., Burlington
JULIAN P. LEVINSON, M.D., Pittsburgh
MORTON H. MAXWELL, M.D., Los Angeles
MILTON H. PAUL, M.D., Chicago
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
WAYNE R. ROGERS, M.D., Portland
ELLIOT L. SAGALL, M.D., Boston
SHELDON SHEPS, M.D., Winnipeg

BLOOD COAGULATION AND THROMBOEMBOLISM

Sise, H. S., Lavelle, S. M., Adamis, D., and Becker, R.: Relation of Hemorrhage and Thrombosis to Prothrombin during Treatment with Coumarin-Type Anticoagulants. New England J. Med. **259**: 266 (Aug. 7), 1958.

The authors point out the failure of the Quick test to predict hemorrhage and thrombosis in some patients under long-term anticoagulant therapy with coumarin-type derivatives. The response of 5 patients given warfarin intravenously indicated that the Quick test measures mostly proconvertin and is influenced very little by the circulating levels of prothrombin, Stuart factor, and plasma thromboplastin component. The prothrombin concentrations and Quick times of 84 patients on phenindione over the course of 18 months were determined. In half the patients the 2 tests varied so that the Quick time could not be relied upon to derive an estimate of prothrombin. In this series there were 23 bleeding episodes and 10 possible thrombotic episodes. These episodes correlated quite well with the prothrombin concentration but poorly with the Quick time. These findings indicate that both the Quick time and the prothrombin concentration should be measured in the management of patients under prolonged anticoagulant treatment. The therapeutic range is considered to lie at a prothrombin concentration of 12 to 25 per cent when the Quick time is under 40 seconds.

SAGALL

Aarseth, S., and Lange, H. F.: The Influence of Anticoagulant Therapy on the Occurrence of Cardiac Rupture and Hemopericardium Following Heart Infarction. I. A Study of 89 Cases of Hemopericardium (81 of Them Cardiac Ruptures). Am. Heart J. **56**: 250 (Aug.), 1958.

Data are presented concerning 89 patients with hemopericardium found in 1,229 autopsies of a total of 1,303 patients who died of myocardial infarction at the Ulleval Hospital in Oslo, Norway, during the period of January 1, 1945 to July 1, 1956. Of this group 81 had myocardial rupture, 3 had rupture of the aorta, and 5 showed hemopericardium without demonstrable local cause. These 5 cases occurred among the 33 patients receiving anticoagulant therapy. Observations in this series indicated that anticoagulant therapy increased the risk of hemopericardium, with or without cardiac rupture, largely because of an overdose of anticoagulants.

SAGALL

Lange, H. F., and Aarseth, S.: The Influence of Anticoagulant Therapy on the Occurrence of Cardiac Rupture and Hemopericardium Following Heart Infarction. II. A Controlled Study of a Selected Treated Group Based on 1,044 Autopsies. Am. Heart J. **56**: 257 (Aug.), 1958.

In an autopsy study of fatal cardiac infarction, 69 patients receiving effective anticoagulant therapy were compared with a group of 72 control patients of corresponding age and sex in regard to the incidence of hemopericardium. The in-

idence of hemopericardium (1 patient) or myocardial rupture (14 patients) in the treated group was about twice as large (15 patients out of 69) as in the control group (8 patients out of 72).

SAGALL

Priest, E. M., and Pauli, H. G.: Phenprocoumon (Marcumar). I. An Agent for Short-Term Anticoagulant Therapy. Am. J. Cardiol. **2**: 61 (July), 1958.

A brief experience with phenprocoumon therapy of acute thromboembolic conditions in 160 hospitalized patients is described. The agent was given in daily oral doses aimed at prolonging the Quick one stage prothrombin time to 20 to 35 seconds. No thromboembolic breakthrough was detected during therapy. There were 4 minor and 2 major hemorrhages associated with the prothrombinopenia, and the latter regularly responded to vitamin K or K_1 administration. It was concluded that phenprocoumon is a satisfactory drug for short-term anticoagulation.

ROGERS

Tudhope, G. R., Cohen, H., and Meikle, R. W.: Alopecia following Treatment with Dextran Sulphate and Other Anticoagulant Drugs. Brit. M. J. **1**: 1034 (May 3), 1958.

Pharmacologically, dextran sulfate resembles heparin in its action but has a more prolonged anticoagulant and greater cumulative effect. The commonest toxic effect of dextran is transient alopecia, which appears several weeks after treatment is stopped. The authors observed severe alopecia in 8 of 15 patients who were followed for at least 3 months after receiving 90,000 or more units of dextran sulfate. In 3 of these patients, alopecia was not apparent until 2 months after the end of treatment. The incidence of alopecia is much less with smaller doses of dextran and, in fact, in this study it occurred in only 2 of 12 patients who received less than 70,000 units of dextran sulfate along with a coumadin anticoagulant. Of 60 patients treated with heparin and a coumadin anticoagulant, 3 reported mild or moderate loss of hair following therapy. Diarrhea and depression of the platelet count were also noted in a few patients who received a large total dose of dextran sulfate. The mechanism by which dextran sulfate produces its effect on hair growth is unknown. It is suggested that heparin possibly interferes with the metabolism of the naturally occurring sulfated polysaccharides or the sulfur containing amino-acids. The toxic effects of dextran, namely: alopecia, diarrhea, thrombocytopenia and anorexia are similar to the effects produced by whole-body irradiation, nitrogen mustard, and other antimitotic substances. In this respect, both heparin and dextran are probably antimitotic too. Furthermore, a heparin-like substance may be present in the blood of man following therapeutic doses of nitrogen mustard and in the blood of animals after whole-body irradiation.

KRAUSE

CONGESTIVE HEART FAILURE

Wirth, W.: A New Anti-Carbonic Anhydrase Diuretic. German Med. Monthly **3**: 144 (May), 1958.

Results of administration to animals of diphenylmethane-4-4′-disulphonamide (Nirexon) a new carbonic anhydrase inhibitor are reported. In prehydrated rats oral administration of the drug in dosage of 30 mg. per Kg. of body weight increased diuresis by 40 per cent after 3 hours, 57 per cent after 6 hours, and 37 per cent after 22 hours when compared with the control values in the same animals. Maximal diuretic activity was obtained with a dose of 50 mg. per Kg. of body weight, when maximal blood levels of the drug were reached in 3 or 4 hours. No unpleasant or harmful side effects were observed in acute and chronic experiments with the drug in dogs, cats, rabbits, and rats.

SAGALL

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Bain, R. C., Edwards, J. E., Scheifley, C. H., and Geraci, J. E.: Right-Sided Bacterial Endocarditis and Endarteritis: A Clinical and Pathologic Study. Proc. Staff Meet. Mayo Clin. **33**: 182 (April), 1958.

Bacterial endocarditis has a definite predilection for the left side of the heart. The incidence of isolated right sided bacterial endocarditis is about 5 per cent. Twenty-three patients with bacterial endocarditis or endarteritis in which the vegetations were predominantly or exclusively on the right side of the heart or in the pulmonary artery are reviewed. A clinical diagnosis was made in only 26 of these patients, and in only 3 was the location of the vegetations correctly determined. The absence of a significant cardiac murmur in 15 of the 23 patients was the greatest single diagnostic obstacle. In no patient without a murmur was the disease correctly diagnosed. The relative incidence of various symptoms and signs in the patients without a murmur was as follows: fever 93 per cent, leukocytosis 92 per cent, pulmonary symptoms 87 per cent, anemia 79 per cent, positive blood cultures 73 per cent,

hematuria 70 per cent, and splenomegaly 7 per cent. From this data it is apparent that signs of infection, evidence of pulmonary infarction without disease in the peripheral or pelvic veins, anemia, positive blood cultures, and microhematuria should always suggest the diagnosis of right-sided bacterial endocarditis, despite the absence of a significant cardiac murmur. Extensive pulmonary infarction with generalized sepsis was by far the most common cause of death in this series (74 per cent).

KRAUSE

Laconi, A.: The Dynamics of the Left Ventricular Border in Chronic Constrictive Pericarditis: An Analytic Roentgenkymographic Study with Remarks on the "Flat Top and V" Electrokymographic Pattern. Am. Heart J. **56**: 73 (July), 1958.

A group of 16 subjects with chronic constrictive pericarditis, including 12 operated upon by pericardiectomy, were studied by analytic roentgenkymography. The results of this method of study of the left ventricular border were compared with those of electrokymography. In 9 patients the tracings on the left ventricular border showed absence of any cyclic phenomena with a straight line, due to standstill of the ventricular border. In 7 cases the cycles were clearly evident but their contour was greatly deformed, showing a "trapezoid" pattern corresponding to the diastolic "flat top and V" pattern described in the electrokymogram. These tracings exhibited a steep lateral movement during rapid filling, and standstill during slow filling. The steepness of the slope of the systolic descending limb was equal to that of the ascending limb of rapid filling resulting in a trapezoid form to the pattern. On the basis of the kymoanalytic results it is suggested that the nonuniform findings obtained by electrokymography in chronic constrictive pericarditis may be explained by the facts that the trapezoid is not a constant finding in these cases but is only statistically prevalent and that even in those cases with a trapezoid type of left ventricular movement, the electrokymogram may be deformed by variations in the density of the paracardiac shadows.

SAGALL

Selye, H.: Production by Various Fats of Myocardial Necroses in Humorally Conditioned Rats. Proc. Soc. Exper. Biol. & Med. **98**: 61 (May), 1958.

Highly active corticoids, such as 2α-methyl-9α-chlorocortisol (Me-Cl-COL)+ plus sodium phosphates (Na_2HPO_4, NaH_2PO_4), invariably produce infarctoid lesions in the myocardium of the rat. The author used these chemicals in conjunction with animal, plant, and mineral oil. The degree of myocardial necrosis and nephrocalcinosis normally produced by the combined treatment with Me-Cl-COL and Na_2HPO_4 was considerably increased by the administration of plant and animal fats, but uninfluenced by the mineral oil.

KRAUSE

Giraud, G., Latour, H., Puech, P., Olivier, G., and Hertault, J.: Filarial Cardiopathy. Hemodynamic Study. Arch. mal. coeur **51**: 546 (June) 1958.

Cardiac failure with marked eosinophilia, in a patient known to have filariasis, is reported. The favorable effect of treatment with corticoids is described; specific treatment was introduced only after prolonged use of the corticoids. The regression of the electrocardiographic signs of subendocardial involvement is illustrated. The early dip and plateau of the right ventricular pressure curve and the M contour of the right atrial tracing, typical of the constrictive syndrome, persisted however after compensation. It was suggested that the constriction was not the most important factor of failure. A delay between electrical and mechanical systole was observed in this patient and was found also in other published reports of the constrictive syndrome of endocardial origin. This delay was not found in constrictive pericarditis. The patient was described as an example of fibroplastic parietal endocarditis due to an allergic reaction caused by filariasis.

CALABRESI

HYPERTENSION

Redleaf, P. D., and Tobian, L.: The Question of Vascular Hyper-Responsiveness in Hypertension. Circulation Research **6**: 185 (March), 1958.

Spirally cut strips of aorta from hypertensive rats did not show hyperresponsiveness to norepinephrine, compared to the aorta from normotensive rats. There were 2 distinct factors that might cause an apparent hyperresponsiveness of hypertensive subjects to pressor agents in the absence of an actually greater shortening of circular smooth muscle fibers. First, waterlogging and hypertrophy, by increasing the wall thickness of arterioles, could produce apparent hyperresponsiveness. Second, a slight decrease in cross sectional areas of the arteriolar lumen as a result of possible preexisting smooth muscle contraction could also create a situation of apparent hyperresponsiveness.

AVIADO

Arnold, O. H., and Bock, K. D.: The Problem of Postnephritic Hypertension. German Med. Monthly **3**: 175 (June), 1958.

In 14 patients with acute glomerulonephritis who were observed for many years it was noted that the urinary signs of nephritis regressed completely, while arterial hypertension—indistinguishable from essential hypertension—became progressively more prominent. The urinary concentration tests were normal in all patients and there was no retention of urea. Paraaminohippuric acid and inulin clearances were normal in 7 cases and abnormal in 7. In this latter group the abnormality in the clearance tests was considered to represent a residual defect after healing of the nephritis. The persistent hypertension in these patients with its independent course after healing of the renal lesion is termed "postnephritic hypertension" by the authors. This term is meant to highlight the point of practical importance that persistent hypertension may occur after acute glomerulonephritis in the absence of clinical signs of an inflammatory renal lesion. A hypothesis is also suggested for the pathogenesis of hypertension in the course of chronic glomerulonephritis.

SAGALL

Imhof, P., and Hürlimann, A.: Results of Comparative Indirect (Auscultatory) and Direct (Intraarterial) Blood Pressure Measurements. Cardiologia **33**: 2, 1958.

The authors compared blood pressure values obtained with the cuff method and by intraarterial puncture in 40 persons 19 to 80 years old including individuals with normal cardiovascular findings as well as patients with hypertension and arteriosclerosis of varying degrees. The pressures were recorded simultaneously with a commercial mercury manometer (Erka) with a cuff of 13-cm. width on 1 arm and with a stiff polyethylene catheter connected to a strain gage electromanometer (Elema) in the other arm. Further details of the technic and of precautions are outlined. The results were as follows: in normotensive individuals systolic figures obtained by the cuff method proved approximately correct. In hypertensive patients values of the systolic cuff pressure were too low in proportion to the degree of pressure elevation. Almost without exception, diastolic pressures determined by the cuff method were higher than those of intraarterial measurements. The magnitude of errors varied in individual persons with alterations in their circulatory dynamics.

PICK

Chesley, L. C., and Valenti, C.: The Evaluation of Tests to Differentiate Pre-Eclampsia from Hypertensive Disease. Am. J. Obst. & Gynec. **75**: 1165 (June), 1958.

Patients were selected on the basis of clinical evidence for the diagnosis of pre-eclampsia or hypertensive disease complicating pregnancy: there were 15 thought to have pre-eclampsia and 16 with uncomplicated hypertension. Numerous tests were done, including the following, in order to differentiate between these 2 entities: cold pressor test, response to vasopressin, response to intravenous tetraethyl ammonium chloride (TEAC), sodium tolerance test, and renal clearance of urate. The blood pressure responses to the cold pressor test and to intravenous TEAC were not significantly different in the 2 groups and were of no differential diagnostic value. In pre-eclampsia the mean rise in blood pressure after subcutaneous injection of vasopressin was greater than in hypertensive women. The mean renal clearance of urate was depressed in pre-eclampsia as was the mean urinary concentration of sodium after sodium loading compared to the mean values of pregnant hypertensive women. Although the average values differed in the last 3 tests, there was considerable overlapping of the responses from group to group. None of the tests was considered specific for definite diagnosis. The situation was not improved by using the 3 latter tests in conjunction, for any 1 test may disagree with the other 2.

SHUMAN

Freedman, P., Moulton, R., and Spencer, A. G.: Hypertension and Diabetes Mellitus. Quart. J. Med. **27**: 293 (April), 1958.

Blood pressure was measured in 1,100 diabetic patients. Hypertension was defined as a diastolic blood pressure of 100 mm. Hg or more after an arm circumference allowance had been applied. The incidence of hypertension increased with age to a maximum of 92 per cent of female and 81 per cent of male diabetic subjects at 70 to 79 years. The clinical impression of an increased incidence of hypertension among diabetic persons was shown to be due to the abnormal age and sex distribution of the diabetic population. From 10 to 69 years of age there was no significant difference in the incidence of hypertension in the diabetic as compared with a nondiabetic population. Only at ages 70 to 79 years was an increased incidence of hypertension found in the diabetic group. Severe hypertension was rare in diabetes. Nephropathy was diagnosed in 27.5 per cent of hypertensive diabetic patients.

KURLAND

Deming, Q. B., Hodes, M. E., Baltazar, A., Edeira, J. G., and Torosday, S.: The Changes in Concentration of Cholesterol in the Serum of Hypertensive Patients During Antihypertensive Therapy. Am. J. Med. **24:** 882 (June), 1958.

The concentration of serum cholesterol was measured in 21 patients with advanced hypertensive disease in control periods and during administration of reserpine, hydralazine, and ganglionic-blocking agents. Reserpine, in the unusually large doses used produced no consistent significant fall in serum cholesterol but hydralazine, chlorisondamine, and mecamylamine resulted in a significant sustained fall. The rice diet may produce a similar change. It is suggested that there may be a direct relation between blood pressure and cholesterol level.

KURLAND

Baldwin, D. S., Biggs, A. W., Goldring, W., Hulet, W. H., and Chasis, H.: Exaggerated Natriuresis in Essential Hypertension. Am. J. Med. **24:** 893 (June), 1958.

The basal sodium excretion and the response to a challenge with hypertonic sodium chloride were studied in 22 hypertensive subjects and 13 normotensive individuals free of cardiovascular disease. Sodium and solute excretion in response to a challenging infusion were significantly greater in hypertensive than in normotensive patients although there was no difference in basal sodium excretion. A natriuretic response similar to that of hypertensive patients could be induced in normotensive patients by prolonging the infusion of hypertonic saline to 2 hours. Nine of 16 hypertensive patients also excreted increased sodium following hypotonic infusion of inulin and para-aminohippuric acid. Low sodium excretion in hypertensive patients during salt deprivation and abolition of the exaggerated natriuresis during salt deprivation indicated that the renal tubule in the hypertensive kidney could conserve salt effectively.

KURLAND

Lee, R. E., and Schneider, R. F.: Hypertension and Arteriosclerosis in Executive and Nonexecutive Personnel. J.A.M.A. **167:** 1447 (July 19), 1958.

It has long been a popular belief that there is association between cardiovascular disease and strain of executive responsibility. Few articles contain objective factual data to substantiate this thesis. A comparison was made between 1,171 male executives and 1,203 nonexecutives (of whom 563 were female) observed over periods averaging 5 years in respect to evidence of arteriosclerosis and hypertension. This study revealed no increase in incidence of either hypertensive or arteriosclerotic disease in the executive class. Hypertension appeared more frequently in subjects at lower levels of business duties. Arteriosclerotic disease as a whole occurred at a significantly lower rate among executives than in persons in other work groups of comparable age and employed in the same office building. Three factors that might be concerned in the etiology are: success in career attainment often goes hand in hand with good health, the possibility that with greater financial income the individual is able to afford a higher standard of living and more complete medical care, with executive education and insight, these individuals may realize the value of "escape valves" and develop outside avenues of expression, such as hobbies. It appears that at least part of the recent emphasis on the dangers of executive life with reference to the vascular system may be based more on knowledge of the exceptions rather than of the rule.

KITCHELL

METABOLIC EFFECTS ON CIRCULATION

Welch, G. H., Jr., Braunwald, E., Case, R. B., and Sarnoff, S. J.: The Effect of Mephentermine Sulfate on Myocardial Oxygen Consumption, Myocardial Efficiency and Peripheral Vascular Resistance. Am. J. Med. **24:** 871 (June), 1958.

Mephentermine sulfate was administered in 4 types of canine preparations (intact animal, open chest animal, and exchange maintained isolated heart) to ascertain its effect on myocardial contractility, peripheral vascular resistance, myocardial oxygen consumption, and myocardial efficiency. Mephentermine produced a positive inotropic and chronotropic cardiac effect. In contrast to metaramine, it had little effect on total peripheral resistance. It produced a striking elevation of ventricular function curves and consistently lowered atrial pressures. It increased myocardial oxygen consumption and decreased external efficiency when it was administered at a filling pressure of 12.3 cm. of water but decreased myocardial oxygen consumption and increased efficiency at a filling pressure of 41.4 cm.

KURLAND

McCreary, A. B.: The Plasma Antidiuretic Activity in Toxemia of Pregnancy. Am. J. Obst. & Gynec. **75:** 1174 (June), 1958.

A bioassay method was employed to determine the plasma antidiuretic hormone (ADH) activity in patients with toxemia of pregnancy. The urinary output of albino rats was determined after

ydration, following which the animals were re-ydrated and injected with 2.5 cm. of test plasma nd the urinary output was compared to that of ne control period. Nonpregnant hydrated females ere employed to provide data thought to repre-nt the irreducible minimum of ADH activity in uman subjects as revealed by this method. tandard curves were obtained by dilutions of nown amounts of Pitressin made with plasma rom the hydrated nonpregnant female as the dil-nt. The normal-term pregnant patient exhibits ry little antidiuretic activity. Mild pre-eclampsia evealed a slight difference from the normal. In vere pre-eclampsia the highest level of ADH tivity was encountered. Patients with eclamp-ia revealed a high level of ADH activity, slightly ss than those with pre-eclampsia. Hydration herapy for eclampsia sharply depressed ADH tivity in 6 of the patients to levels indistin-uishable from those of the normal-term pregnant atient.

SHUMAN

Genest, J., Koiw, E., Nowaczynski, W., and Leboeuf, G.: Further Studies on Urinary Aldosterone in Human Arterial Hypertension. Proc. Soc. Exper. Biol. & Med. **97**: 676 (March), 1958.

Urinary aldosterone excretion was studied in human arterial hypertension of varied etiology. Increased aldosterone excretion was found in approximately 55 per cent of the patients studied. In particular, a very significant difference between the mean aldosterone excretion of patients with essential, renal, or malignant hypertension as compared with normal subjects was demonstrated. Two patients with early asymptomatic hypertension had much greater fluctuations in serial daily aldosterone determinations when compared with normal subjects. No correlation could be demonstrated between aldosterone excretion and sodium intake. However, many hypertensives had a higher aldosterone output on a lower potassium intake than normal subjects. The authors suggest that their data supply additional evidence for an adrenal cortical disturbance in cardiovascular disease.

KRAUSE

Szekeres, L., Lenard, G., and Soti, J.: The Action of Various Metabolic Intermediates on Oxygen Consumption of Normal and Hypoxic Heart Muscle Slices. Arch. internat. pharmacodyn. **115**: 141 (May), 1958.

A study is presented of the oxygen consumption of heart muscle slices prepared from normal and from hypoxic albino rats and incubated in a modified Krebs-Herzeleit solution, with and without added different substrates. Hypoxia was produced by placing the animals in closed vessels containing 5 per cent sodium hydroxide to absorb carbon dioxide. The substrates used were glucose, sodium pyruvate, sodium fumarate, sodium succinate, sodium lactate, sodium acetate, and sodium citrate. Only succinate and fumarate increase the oxygen uptake of the slices obtained from normal hearts; all the added substrates proved effective when slices obtained from hypoxic animals were used. It is suggested that hypoxia decreases the oxygen consumption of the heart because it produces depletion of stores of the substrates used in these experiments.

CALABRESI

Szekeres, L., Faller, J., and Török, T.: The Effect of Hypothermia and Drugs of the High Energy Phosphate and Glycogen Content of the Rat Heart. Arch. internat. pharmacodyn. **115**: 131 (May), 1958.

Experiments are reported on the effect of hypoxia and of hypothermia on the content of phosphocreatine, adenylpolyphosphates, and glycogen of the heart of albino rats. The effect of drugs used to eliminate shivering during induction of hypothermia was also investigated. The hearts of animals anesthetized with urethan and rapidly cooled in ice-cold water showed little difference from controls in high energy phosphate and glycogen content. Evipan and Relaxil (Myanesin), in doses well tolerated by the uncooled controls, proved to be toxic for the animals in hypothermia. It is suggested that this is due to the slow elimination of these drugs in the hypothermic state; their effect may instead be lower rather than higher if the drugs are administered after cooling, due to their slow absorption. Smaller doses, added to urethan, prevented shivering during induction of hypothermia; these combinations produced a decrease in the phosphocreatine level even in uncooled rats; the depletion was still higher in hypothermia. Hypothermia, induced without premedication by exposing the animals to hypoxia (method of Giaja), produced a considerable decrease in the high-energy phosphate and glycogen stores. Hypoxia, obtained by exposing the animals to reduced barometric pressure, also caused depletion of high-energy phosphates and glycogen; preliminary cooling markedly decreased this effect of hypoxia.

CALABRESI

Szekeres, L., Lenard, G., Banhidy, F., and Török, T.: The Effect of Epinephrine on Myocardial Metabolism of Normal and Hypoxic Rats. Arch. internat. pharmacodyn. **115**: 150 (May), 1958.

The effect of epinephrine on oxygen consumption, anaerobic glycolysis, and high-energy phosphate content of slices of heart of normal and hypoxic rats was studied. Methods used in these investigations have been reported in previous articles. Epinephrine at 10^{-6} M concentration stimulated myocardial metabolism; higher concentration produced no significant increase in oxygen uptake. Glucose uptake was also increased; glycolysis was depressed; high-energy phosphate content was decreased. These effects were more marked when slices from hypoxic animals were used. Also on the basis of data from others, it appeared that epinephrine decreased the efficiency of the heart muscle. As oxygen uptake was increased and high-energy phosphates was decreased, the question was proposed, but not solved, that epinephrine may act as an uncoupling agent. It is pointed out that the increased effect of epinephrine in hypoxia may be a factor in the pathogenesis of angina pectoris.

CALABRESI

Humerfelt, S., Muller, O., and Storstein, O.: The Circulation in Hyperthyroidism: A Cardiac Catheterization Study before and after Treatment. Am. Heart J. **56**: 87 (July), 1958.

The influence of thyrotoxicosis on the circulation was studied in 32 patients by means of cardiac catheterization. After treatment with antithyroid drugs 15 patients were recatheterized. The results confirm the findings of previous investigators that the increase in cardiac output in hyperthyroidism is due primarily to an increased heart rate with changes in stroke volume and arteriovenous oxygen difference playing no significant role in most cases. However, in those patients with a very high cardiac output, a decrease in stroke volume may be seen after treatment. The increased cardiac output in hyperthyroidism is accompanied by an elevation of systolic pressure in the right ventricle and pulmonary artery pulse pressure. Effective treatment leads to a reduction in cardiac output together with a decrease in the systolic pressure and the pulse pressure in the pulmonary and systemic circulations.

SAGALL

Lostroh, A. J.: Relationship of Steroid and Pituitary Hormones to Myocardial Calcification in the Mouse. Proc. Soc. Exper. Biol. & Med. **98**: 84 (May), 1958.

Calcification of the myocardium of intact female mice was consistently produced by the administration of hydrocortisone at daily dose levels above 0.25 mg. The preferential site for the calcification to occur was the intraventricular septum, and as the calcification became more extensive, the right ventricle was also effected but the left ventricle was rarely involved. The concurrent administration of testosterone to the female aggravated the condition; however, ovariectomy afforded no protection to the heart. In the hypophysectomized mouse neither hydrocortisone nor ACTH was effective in inducing the deposition of calcium in the myocardium. The administration of growth hormone with hydrocortisone or ACTH aggravated the condition. Lectogenic hormone, DOCA, and Estradiol had no effect.

KRAUSE

Grabner, G., Kaindl, F., Kohn, P., and Neumayr, A.: The Effect of Adrenaline and Nor-Adrenaline on Hepatic Blood Flow. Ztschr. Kreislaufforsch. **47**: 405 (May), 1958.

In 24 dogs intravenous injections of epinephrine or norepinephrine caused a temporary increase of blood flow in the hepatic vein, measured with a thermocatheter, sometimes followed or preceded by a slight decrease. This decrease was partly counteracted by the elevation of systemic arterial blood pressure. The increase in blood flow seemed to result from reflex vagal vasodilatation; it was inhibited by vagotomy but not by denervation of the carotid sinus. The increase in right atrial pressure, which often accompanied the increase in hepatic blood flow, was attributed to smooth muscle contraction in the hepatic sheath. Norepinephrine usually elevated the portal venous pressure less than epinephrine.

LEPESCHKIN

Goodford, P. J.: Metabolic Factors and Ventricular Fibrillation. Brit. J. Pharmacol. **13**: 144 (June), 1958.

Isolated rabbit hearts were perfused with various modifications of Ringer's solution in order to study the ease of electric induction and duration of ventricular fibrillation. Fibrillation was favored by a reduction in potassium concentration (e.g., below 5.6 mEq. per Liter), by the addition of sodium azide, sodium monoiodoacetate, or sodium flouride, and by prolonged omission of glucose from the perfusate. This effect was reversed by adding glucose, mannose, or sodium pyruvate but not by sodium L (—) lactate; by a temperature of 37 C. as contrasted with one of 32 C.; and by the addition of epinephrine. Fibrillation could not be induced in the absence of

oxygen or of calcium or in the presence of twice-normal concentrations of potassium.

ROGERS

PHYSICAL SIGNS

Burnard, E. D.: A Murmur from the Ductus Arteriosus in the Newborn Baby. Brit. M. J. **1**: 806 (April 5), 1958.

One hundred healthy babies were examined in the early hours of life. A characteristic murmur that lasted for a short time was audible in 37 patients. Babies who had shown signs of asphyxiation during delivery had ductus murmurs at the first examinations more commonly than those who cried and breathed normally within 3 minutes. The murmur that was heard resembled that of the patent ductus in quality, conductivity, and phonocardiographic properties and hence was attributed to flow from the aorta to the pulmonary arteries through a patent ductus. The authors draw an analogy between the newborn lamb, where the ductus is partly contracted and a continuous murmur is heard. They conclude that in the babies examined, mild asphyxia at birth was responsible for the majority of the murmurs and only a minority of the murmurs were related to a body temperature above normal.

KRAUSE

Matthews, M. B., and Hampson, J.: Hepatojugular Reflex. Lancet **1**: 873 (April 26), 1958.

The mechanism of the hepatojugular reflex was investigated by measuring changes in the central venous and intrathoracic pressure to assess the value of the test as an early sign of cardiac failure. The filling pressure (intrathoracic plus central venous pressure) rose in all subjects, being highest in those with cardiac failure. The effect on central venous pressure was largely determined by the simultaneous change in intrathoracic pressure. This was unpredictable, and it was therefore concluded that the observation of jugular venous pressure while applying abdominal pressure was unreliable as an early sign of cardiac failure. In emphysema, the intrathoracic pressure response was more predictable but here the reflex was regarded more as an indication that the emphysema was severe than that there was cardiac failure.

KURLAND

PULMONARY DISEASES

Steenburg, R. W., Warren, R., Wilson, R. E., and Rudolf, L. E.: A New Look at Pulmonary Embolectomy. Surg. Gynec. & Obst. **107**: 214 (Aug.), 1958.

The surgical removal of a large pulmonary embolus was attempted first in 1908 by Trendelenburg. Subsequently, 12 such patients have been reported to survive satisfactorily. However, owing to the brief amount of time available preoperatively and considering the high mortality and morbidity rates, the procedure has lost vogue, particularly since the advent of anticoagulants 15 years ago. The authors, after 14 failures, describe the first successful American experience with the operation. Two 10 cm. long emboli were removed from the right pulmonary artery of a 64 year old woman within 55 minutes after onset of syncope and shock. Although complications occurred including ventricular fibrillation and later acidosis, myocardial infarction, and hemiparesis, she recovered with minimal sequelae. The operation is recommended for the infrequent patient in whom the diagnosis is reasonably clear, who has no major complicating disorder and who has not reached an agonal state.

ROGERS

Weidner, M. G., Jr., and Light, R. A.: Role of the Autonomic Nervous System in the Control of the Pulmonary Vascular Bed. Ann. Surg. **147**: 895 (June), 1958.

By use of a technic for producing localized pulmonary emboli by means of plastic spheres of varying sizes introduced through a balloon cardiac catheter placed into the pulmonary artery, the authors found that in the dog the pulmonary hypertension, peripheral hypertension, hyperpnea, and bradycardia associated with pulmonary embolism were reflex in nature. This reflex was initiated only in vessels no larger than 25 to 100 μ in diameter. It was mediated through the sympathetic nervous system. The hyperpnea observed after pulmonary embolism appeared to be mediated through the vagus nerve, since it was not produced following vagotomy. The fact that similar physiologic phenomena were also produced by massive emboli with large particles indicated that such emboli must induce a widespread mechanical blockage of the pulmonary tree.

SAGALL

ROENTGENOLOGY

Brasche, H.: Contribution to the Technique of Aortography. Fortschr. Geb. Röntgenstrahlen **88**: 669 (June), 1958.

Dye injection into the lower abdominal aorta was made best through a lateral approach toward the body of the third lumbar vertebra, by means of the Deneke cannula, which has a lateral opening and thus avoids accidental direct injection into the renal arteries. Injection of procaine previous to aortography prevented vascular spasm.

General anesthesia with barbiturates was preferable as it led to muscle relaxation, which permitted better feeling of the progress of the cannula and as it allowed repetition of the aortography even after accidental para-aortic injection. Of 30 aortographies none resulted in serious complications. In 1 patient with occluded aorta the inferior vena cava was filled with dye, without causing any untoward effects.

LEPESCHKIN

Kaindl, F., Mannheimer, E., and Thurnher, B.: Lymphangiography and Lymphadenography in Man. Fortschr. Geb. Röntgenstrahlen **89**: 1 (July), 1958.

The results of lymphangiography in 140 patients were reported; the technic used has been described by Kinmonth and also by the authors. In most cases only the lymphatic vessels of the lower limbs were studied. Possible pitfalls of the method used were pointed out. Primary changes of the lymphatic vessels were classified as hypoplastic and lymphectatic: these were conveniently subdivided into lymphedema congenitum, precox, and tardum; Milroy's disease, of which no case was observed in this study, is a separate entity. Secondary changes may be post-thrombophlebitic, post-traumatic, resulting from roentgen irradiation, or from pelvic inflammation. These changes were described in detail. It was pointed out that the lymphatic post-thrombophlebitic changes appeared only if there was edema of the leg; this was interpreted as due to occlusion of the deep lymphatic vessels and increased flow and possibly also inflammation of the superficial lymphatics. With reference to previous reports on lymphadenography, it was found that the lymph nodes in patients with lymphatic leukemia were enlarged and showed a marked enlargement of the "empty centers." In Hodgkin's disease the afferent lymph vessels were enlarged and the nodes had lost their characteristic structure. In lymphosarcoma, reticulosarcoma, melanoma, or metastatic carcinoma the dye collected in small peripheral lakes and the efferent vessels were not injected. After radiation or infiltration therapy the lymphatic nodes were not injected. Although these changes were quite typical, more extensive experience is necessary before diagnostic criteria are established.

CALABRESI

Hallerbach, H., and Schaede, A.: The Diagnosis of Complete Transposition of the Pulmonary Veins. Fortschr. Geb. Röntgenstrahlen **89**: 152 (Aug.), 1958.

Twenty cases of complete transposition of the pulmonary veins were reported. The finding of similar oxygen content in blood samples from the right atrium and from a peripheral artery was evidence of complete admixture. The diagnosis of localization of the malformation, and of accompanying defects may be difficult. Cardiac catheterization and angiography were employed; measurement of oxygen content of multiple blood samples and selective angiography may add valuable information toward a precise topographic diagnosis. Only in cases of persistent left superior vena cava draining the pulmonary veins were the findings always characteristic.

CALABRESI

Moder, H.: On the Radiologic Diagnosis of Aneurysmatic Changes of the Pulmonary Artery and Its Differentiation from Hilar Shadows due to Tumors. Fortschr. Geb. Röntgenstrahlen **89**: 172 (Aug.), 1958.

Enlargement and aneurysmatic dilatation of the pulmonary artery and its main branches may occur in congenital malformations with increased pulmonary blood flow, in chronic pulmonary parenchymal diseases causing pulmonary arterial hypertension, rarely in specific arteritic diseases, or finally in pulmonary arteriosclerosis. The importance of a correct diagnosis, in view of the serious prognosis of the aneurysm, was stressed; as other signs were lacking or nonspecific, the diagnosis was essentially based on radiologic findings. In most patients routine radiography, and fluoroscopic and tomographic studies were characteristic; roentgenkymographic findings were briefly reported. The differentiation from hilar enlargement due to tumors may prove difficult. Four cases, 1 of hilar tumor and 3 of aneurysmatic dilatation were presented.

CALABRESI

Linko, E., and Sysimetsï, E.: Clinical and Radiological Aspects of Calcification of the Mitral Region. Brit. Heart J. **20**: 329 (July), 1958.

Tomograms (right and left atrial oblique projections at 20°) uncovered 24 calcified mitral valves in 68 consecutive unselected cases of rheumatic heart disease. Calcification was more common in those with stenosis than in those with regurgitation. It was not related to age although it was not seen below 30 years or within the first 10 years after rheumatic fever. Because such calcification implied degenerative changes in larger areas which may interfere with successful surgery and increase mortality, tomographic examination was necessary for a reliable preoperative evaluation.

SOLOFF

SURGERY AND CARDIOVASCULAR DISEASE

DeBakey, M. E., Cooley, D. A., Crawford, E. S., and Morris, G. C., Jr.: Aneurysms of the Thoracic Aorta. J. Thoracic Surg. **36**: 393 (Sept.), 1958.

The authors report a 7-year experience with resection of thoracic aortic aneurysms in 179 patients. Of these there were 73 aneurysms of the descending aorta, 50 involving the arch, 22 thoraco-abdominal aneurysms, and 34 dissecting aneurysms. Descending thoracic aortic aneurysms were due more often to arteriosclerosis than to syphilis (47 per cent and 32 per cent respectively). The most important feature of excisional therapy was the need for temporary occlusion of circulation through the affected segment, with the attendant risks of the effects of increased vascular resistance on the heart and ischemic damage to the spinal cord. Hypothermia was used for this purpose, but in the last 36 patients a pump bypass method was employed. This helped reduce the mortality rate from 27 per cent to 19 per cent. Other factors influencing mortality are discussed. The graft material currently employed is made of crimped, knitted Dacron. The aortic arch aneurysms (mostly syphilitic) were obviously the most serious ones, and presented a very difficult problem with regard to temporary arrest of the aortic circulation. However, this has been eased somewhat with the development of the crimped Dacron tube for use as a temporary or permanent shunt along with an extracorporeal bypass pump. The total mortality in this group was 56 per cent. Thoracoabdominal aneurysms present the additional problem of involvement of the principal vascular supply of important abdominal organs, with danger of fatal ischemic damage to the kidneys, liver, and gastrointestinal tract during the period of resection and graft replacement. Efforts to overcome this complication have included the use of hypothermia, extracorporeal circulation, and temporary shunts. Recently the crimped, knitted Dacron tube has been employed for the purpose of converting the temporary shunt to the permanent graft. In this series of 22 cases there were operative deaths. Dissecting aneurysms presented difficult problems because of the wide extent of the dissection and the poor general condition of most patients. Contrary to prevailing belief, the aortic arch was involved in only 4 of the 34 cases. In the others, the dissecting process arose in the proximal segment of the descending aorta. The greater frequency of lesions of the descending aorta in necropsy studies is probably explained by the greater likelihood of fatality in these cases, whereas the dissections that start in the descending aorta are more apt to have a subacute course. The ascending aortic dissections were repaired by creation of a re-entry passage above with obliteration of the false passage below. Lesions arising in the descending aorta were treated by excision of the involved segment and graft replacement, sometimes also with obliteration by suture of the false passage below. There were 8 deaths in the 30 cases in this series.

ENSELBERG

MacCuish, R. K.: Cardiac Arrhythmias Following Mitral Valvotomy and Their Management. Acta med. scandinav. **161**: 125, 1958.

This report deals with the incidence and management of cardiac arrhythmias occurring after mitral valvotomy in 492 patients who had a sinus rhythm at the time of surgery. Atrial fibrillation was, by far, the most common arrhythmia, occurring in 91 patients. There were single instances of nodal rhythm, complete atrioventricular dissociation, atrial tachycardia, and ventricular tachycardia, the latter 2 arrhythmias occurring in the same patient. Two patients developed interference dissociation. In the arrhythmias other than atrial fibrillation digitalis appeared to be a definite factor in their production. In these patients, withdrawal of digitalis and administration of potassium chloride orally resulted in a return to sinus rhythm in all but 1 patient. This single failure to return to sinus rhythm occurred in a patient with complete atrioventricular dissociation who died suddenly 7½ hours after the initial onset of the arrhythmia. There was a higher incidence of arrhythmia in the patients with large hearts and in the older age groups. Pulmonary infarction appeared to precipitate 1 instance of atrial fibrillation. In previously undigitalized patients, atrial fibrillation was treated with digoxin. Generally no attempt at conversion of the atrial fibrillation to sinus rhythm was made within 14 days of operation. During this period spontaneous return to sinus rhythm occurred in 13 patients. Conversion to sinus rhythm with the use of both quinidine and Pronestyl was attempted in 71 patients. Sinus rhythm was restored in 57. Sixty-one patients were treated with quinidine, 45 initially and 16 after failure with Pronestyl; 47 of these were successfully reverted to sinus rhythm. Twenty-seven patients were treated with Pronestyl, 23 initially and 4 after failure with quinidine, with success in 10 instances. There were no instances of systemic embolization.

BROTHERS

Weirich, W. L., Paneth, M., Gott, V. L., and Lillehei, C. W.: Control of Complete Heart Block by Use of an Artificial Pacemaker and a Myocardial Electrode. Circulation Research **6**: 410 (July), 1958.

The combined use of an artificial pacemaker and a myocardial wire electrode has been demonstrated to be an effective method of controlling the heart rate when complete heart block is present. The cardiac output and mean aortic pressure of dogs have been restored to preblock levels through the application of repetitive stimuli to the ventricular myocardium. The heart rates of 18 patients with complete heart block following closure of septal defects have been controlled successfully.

AVIADO

Crockett, F. B., and Norman, A. G.: Late Results of Direct Surgery of the Aortic Bifurcation and its Major Branches. Brit. M. J. **1**: 727 (March 29), 1958.

The results of surgery performed on the large arteries, ranging from the aorta to the common femorals, are presented. Thirty patients were studied; 26 came to operation because of thrombotic disease of the aortic bifurcation or 1 or both common or external iliac arteries; 4 had an aneurysm of the aorta. Three different types of surgery were used: replacement with stored homograft, replacement with plastic prostheses, and endarterectomy of the occluded segments. The hospital mortality was 7 per cent and delayed mortality (due directly or indirectly to the operative procedure) added another 7 per cent mortality. Such procedures are recommended to any patient under the age of 60 who has a major arterial occlusion and desires relief from symptoms. If the lesion is localized with reasonably good arteries on either side, direct removal of the thrombus is safe and indicated. If the arterial disease is more widespread, a better long-term result will be obtained by radical resection of the entire aortic bifurcation and bypassing the disease segments on each side with stored homograft. In patients over the age of 60 the likelihood of the coexistence of other atherosclerotic lesions, such as in the coronary blood vessels, makes the procedure less desirable. However, even in these patients who have intense pain or impending gangrene, the benefits of this type of surgery outweigh the risks. When using homograft, it is important to perform an end-to-side, large, lumen type of anastomosis. Furthermore, the authors stress the beneficial effect of repairing the upper of 2 arterial blocks in the same limb. In aortic aneurysm when there is steadily increasing pain, surgery is urgently required, since this is the prelude to rupture of the aneurysm.

KRAUSE

VALVULAR HEART DISEASE

Bakulev, A. N.: Indications and Results of Surgical Treatment of Mitral Stenosis. Khirurgiia **32**: 6, 1956. (Translation of this paper has been furnished by the National Institutes of Health, B. S. Public Health Service, as a part of their Scientific Translation Program.)

Mitral valvuloplasty was performed in 124 patients with mitral stenosis. Preoperative diagnosis was based not only on auscultation, cardiac catheterization and, recently, direct cardiac puncture but also on "cardiohaemodynamography." The latter is a technic that registers the mechanical aspects of cardiac activity—the heart beat, motion of the heart, and the blood mass—by converting mechanical events into an electric record. The result is a complex curve the analysis of which permits accurate measurement of the phases of the cardiac cycle and the efficiency of cardiac action. A number of characteristic signs were revealed that were described as pathognomonic for certain pathologic states. In mitral stenosis, this examination gave more useful information than ballistocardiography, rheocardiography, and electrokymography. Patients were divided into 5 groups on the basis of the severity of symptoms. Mortality was 7.3 per cent in stage II patients, 21 per cent in stage III, and 31.2 per cent in stage IV. Active rheumatic carditis was not regarded as a contraindication. In fact, deteriorating condition in a patient with mitral stenosis and active rheumatism was regarded as an indication for operation. Results in such patients were not different from the usual. Postoperative complications were atrial rupture, ventricular fibrillation, cerebral embolism, and the postcommissurotomy syndrome in which 3 patients died. Twenty-four of 28 patients in stages II and III had good results 1 to 3 years postoperatively but only 12 of 24 patients in stage IV had comparable results.

KURLAND

Killip, T., III, and Lukas, D. S.: Tricuspid Stenosis. Clinical Features in Twelve Cases. Am. J. Med. **24**: 836 (June), 1958.

Clinical experience with 12 patients, age 23 to 52, with tricuspid stenosis, is presented with a detailed report of 5 patients to emphasize the variable manifestations of the lesion. Eleven had rheumatic heart disease with multivalvular involvement. Dyspnea on exertion was universal; orthopnea and fatigue were common; chronic edema occurred in every patient with atrial fibrillation; intraperitoneal fluid was present in half. On examination a low pitched coarse rumbling diastolic murmur was heard in the third to fifth left interspace early in patients with atrial fibrillation and presystolic in patients with sinus

rhythm. In contrast to mitral murmurs, these increased dramatically in intensity during inspiration and decreased during expiration. Pulmonary edema, hepatomegaly occasionally with presystolic pulsation and prominent presystolic pulsation of the external jugular veins were often noted. X-ray revealed enlargement of the right atrium which in 3 patients was gigantic. In sinus rhythm, sharply peaked tall and sometimes prolonged P waves were noted in leads II, V_1, and V_2. Estimation of the area of the tricuspid valve was validated by post mortem planimetry in 1 patient. In 2 patients, the tricuspid valve at necropsy was found less stenotic than the mitral. Although pulmonary pressures were lower when tricuspid stenosis accompanied mitral stenosis than when the latter pas present alone, pulmonary congestive symptoms were frequent.

KURLAND

Cliche, P., Degeorges, M., Colonna, D., and Slama, R.: Mitral Stenosis without Diastolic Rumble. Study of 12 Cases with Surgical or Anatomic Verification. Arch. mal. coeur **51**: 417 (May), 1958.

Of 206 consecutive patients with mitral stenosis no diastolic murmur could be heard on any occasion in 12. All these patients had a very tight stenosis; in 8 patients the valve was calcified and immobile. The pulmonary arterial pressure was 45 to 90 mm., while the electrocardiogram showed marked right ventricular hypertrophy in 11 patients. Ten patients had refractory right ventricular failure. Only 12 patients showed a snapping first sound or reduplicated second sound; these did not show mitral calcifications. Ten patients had a holosystolic mesocardiac murmur, not propagated to the axilla. This murmur was not due to mitral regurgitation, as this was not felt in 5 operated cases, and stenosis was very tight in the rest. In 5 patients it was caused by tricuspid regurgitation, since systolic hepatic pulsation was present, while in others it could result from turbulence in the dilated pulmonary artery. Absence of the diastolic murmur was probably due to the small size of the mitral opening, and possibly also to elevated left ventricular diastolic pressure. Recognition of mitral stenosis, and avoidance of confusion with mitral regurgitation in these cases is of great clinical importance.

LEPESCHKIN

Iesen, K. H., and Warburg, E.: Isolated Aortic Stenosis—The Late Prognosis. Acta med. scandinav. **6**: 437, 1958.

Forty-two patients with isolated aortic stenosis were the subjects of a long-term follow-up study undertaken to contribute further to the description of the natural history of aortic stenosis. This group of patients consisted of 31 men and 11 women with an average age of 52.9 years at the first observation made during the years 1933 to 1949. The follow-up study was done in 1955 and 1956 and the period of observation varied from 6 to 23 years. The clinical diagnosis was not limited to patients presenting the classical signs and symptoms but was also made on patients with a loud, rough, aortic systolic murmur combined with roentgenologic evidence of cardiac enlargement and isoelectric or negative T_1 or left axis deviation. The classical combination of symptoms of aortic systolic murmur, thrill, faint or absent aortic second sound, and anacrotic pulse was found in only 3 of 18 patients (17 per cent) examined at autopsy. Fourteen patients (33 per cent) had a history of rheumatic fever. At the time of follow-up 39 patients had died at an average age of 55.5 years. Thirty seven of the deaths were directly connected with the aortic stenosis or its complications. Cardiac symptoms first occurred at an average age of 47.2 years and there was a mean survival time of 8.8 years after onset of symptoms. Angina pectoris occurred in 52 per cent at an average age of 50.7 years with an average survival time of 4.7 years. Syncope occurred in 22 per cent at an average age of 46.5 years and allowed an average survival of 3.2 years. Congestive heart failure occurred in 23 of 29 patients (79 per cent) followed closely to time of death. The average survival time after onset of congestive failure was less than 1 year. Atrial fibrillation appeared in 3 of 22 patients (14 per cent). Although arrhythmias were not frequent, they were associated with a shortened survival time in the instances in which they occurred. Likewise, definite roentgenologic evidence of cardiac enlargement was associated with a shorter survival time. Systemic arterial embolism did not occur in the series. This study confirms the fact that isolated aortic stenosis is a progressive disease with a grave prognosis and points up the need for a more effective form of therapy.

BROTHERS

OTHER SUBJECTS

Greene, B. A.: Cardiac Output and Total Peripheral Resistance in Anesthesiology. Clinical Applications. J.A.M.A. **166**: 1003 (Mar. 1), 1958.

Observing changes in blood pressure and heart rate alone may not be sufficient in the management of anesthesia in complicated and prolonged operations in "poor risk" patients. The important problems here are the prevention and treatment of circulatory derangements. Stroke-volume formulas are ideal for the investigation of fluc-

tuations in blood pressure. The clinical anesthesiologist can estimate cardiac output and total peripheral resistance with ordinary clinical data. In doing this the author employs evaluation and interpretation of the pressor effect of 90-degree passive elevation of the lower extremities (the "L" position or maneuver). Although here formulated as a diagnostic test, the "L" position (or its equivalent in the counterpressure garment) is more valuable in prophylactic and therapeutic treatment than the "head-down" position in the prevention of venous pooling. The most significant finding of the 90-degree leg raising maneuver is a quick, early rise (fleeting or sustained) in systolic pressure (greater than 10 mm. Hg). This is unequivocal evidence of a rise in cardiac output and reveals venous pooling.

KITCHELL

Wang, K. C., and Howland, W. S.: Cardiac and Pulmonary Evaluation in Elderly Patients before Elective Surgical Operations. J.A.M.A. **166**: 993 (March 1), 1958.

A 12-lead electrocardiogram, a ballistocardiogram, a 1-breath ventilation test for vital capacity, and a 0.5-second expiratory capacity test were incorporated as part of a preanesthetic evaluation program for 482 geriatric patients. Two hundred and twelve of these were between 60 and 90 years of age and in this group the incidence of unfavorable test results as well as postoperative complications was higher than in the younger age group. There was an increase in the incidence of postoperative complications in patients having abnormal ballistocardiograms and ventilatory defects. There was little correlation between electrocardiography and the subsequent course of the individual patient, indicating that the usual method of evaluation of preoperative risk by clinical impression is of little value in geriatric patients. It is believed that evidence of degenerative cardiopulmonary disease may often be elicited in the older age groups and serves as a guide for anesthesia and postoperative therapy.

KITCHELL

Bigler, F. C.: The Morphology of Clubbing. Am. J. Path. **34**: 237 (March-April), 1958.

A study of the pathologic changes in the left thumb of 29 control specimens and 10 specimens from individuals who had clubbing of the fingers is presented. In clubbed fingers the nailbed volume was greater than in the control nailbed (in thickness by about 2 mm.). This was produced by large primitive looking fibroblasts in a reticular network. Surrounding this were extravascular lymphocytes and eosinophils. In a few clubbed fingers there were increased coils of arteriovenous capillary type anastomoses. Edema and thickening of the periosteum were present and in a few cases there was the same type of loosely textured reticular network of primitive fibroblasts on the periosteal surface. In 1 case increased deposition of collagen accounted for the increased thickness. These changes, particularly in the periosteal lesions, are similar to the changes in the bones in hypertrophic osteoarthropathy. The author points this out as a similarity in pathogenesis and a factor for possible better understanding of the clubbing process.

HARVEY

Bär, C. G., Zeilhofer, R., and Heckel, K.: The Cardio-Respiratory Effects of Funnel Chest. German Med. Monthly **3**: 113 (April), 1958.

In 16 patients with funnel chest, pulmonary and cardiac studies showed that the hemodynamic consequences of funnel chest were similar to those of constrictive pericarditis. This finding may explain the cardiovascular features of funnel chest. Although in the advanced stages of this disease right heart failure is a prominent finding, there was no evidence of right ventricular or pulmonary hypertension in the studied cases of this report. Pulmonary functions were found to be within normal limits except for a slight increase in residual volume. The authors point out that severe functional impairment is to be expected only in cases of severe chest deformities and that in these patients surgical intervention may be indicated, if only from the cardiac viewpoint.

SAGALL

Raab, W.: Loafer's Heart. Arch Int. Med. **101**: 194 (Feb.), 1958.

The title refers specifically to our motorized nonexercising population. The author claims that there is statistical and experimental evidence that lack of physical exercise can contribute to the development of degeneration of the myocardium and possibly atherosclerosis. In the "inactive" heart he states that there is a pathologic adrenergic preponderance. This is probably due to an inactivity-induced deterioration of cholinergic counterregulatory mechanisms. If this be true, physical training programs would be one way that the over-civilized and pampered world could escape further myocardial degenerative disease.

KRAUSE

Kartagener, M.: The Significance of Hereditary Conditions in the Genesis of Acquired Heart Disease. Cardiologia **31**: 79 (Fase. 1), 1957.

A number of instances are reported of familial occurrence of coronary thrombosis or coronary

insufficiency, for instance, in parents and children, in siblings, and in twins. In such observations the author sees further evidence that an inherited predisposition must be present for the acquisition of extraneous cardiovascular diseases.

PICK

REVIEWS IN CARDIOVASCULAR DISEASE

Steinberg, J.: Aneurysms of the Thoracic Aorta. Review of Diagnostic and Etiologic Features. Am. J. Cardiol. **1**: 736, (June), 1958.

Kincaid-Smith, P., McMichael, J., and Murphy, E. A.: The Clinical Course and Pathology of Hypertension with Papilloedema (Malignant Hypertension). Quart J. Med. **27**: 117 (Jan.), 1958.

Orabona, M. L., and Albano, O.: Systemic Progressive Sclerosis (or Visceral Scleroderma). Review of the Literature and Report of Cases. Acta med. scandinav. Supplementum 333. Accompanies Vol. 160, 1958.

Lillehei, C. W.: Contributions of Open Cardiotomy to the Correction of Congenital and Acquired Cardiac Disease. New England J. Med. **258**: 1044 (May 22), 1958.

Fazekas, J. F.: Pathologic Physiology of Cerebral Dysfunction. Am. J. Med. **25**: 89 (July), 1958.

McLean, K. H.: The Pathogenesis of Pulmonary Emphysema. Am. J. Med. **25**: 62 (July), 1958.

Pike, G. M.: Polycythemia Vera. New England J. Med. **258**: 1250 (June 19), 1958.

Pike, G. M.: Polycythemia Vera. New England J. Med. **258**: 1297 (June 26), 1958.

Cavert, H. M.: Some Current Views on the Biochemistry and Physiology of Myocardial Contraction. Bull. New York Acad. Med. **34**: 445 (July), 1958.

Wesson, L. G., Jr.: Glomerular and Tubular Factors in the Renal Excretion of Sodium Chloride. Medicine **36**: 281 (Sept.), 1957.

Smith, H. W.: Salt and Water Volume Receptors. An Exercise in Physiologic Apologetics. Am. J. Med. **23**: 623 (Oct.), 1957.

O'Brien, J. R.: Fat Ingestion, Blood Coagulation and Atherosclerosis. Am. J. M. Sc. **234**: 373 (Oct.), 1957.

Orma, E. J.: Effect of Physical Activity on Atherogenesis. An Experimental Study in Cockerels. Acta physiol. scandinav. 41 (Supplement 142), 1957.

Brigden, W.: Uncommon Myocardial Diseases. The Non-coronary Cardiomyopathies. Lancet **2**: 1179 (Dec. 14, 21), 1957.

Schroepfer, G. J., Jr.: Lipid Factors in Atherosclerosis. New England J. Med. **257**: 1223 (Dec. 19, 26), 1957.

Verney, E. B.: Renal Excretion of Water and Salt. Lancet **2**: 1237 (Dec. 21, 28), 1957.

Ahrens, E. H., Jr.: Nutritional Factors and Serum Lipid Levels. Am. J. Med. **23**: 928 (Dec.), 1957.

Errata

Various authors have requested that the following changes be made in their published papers:

DERN, P. L.: Postural hypotension. Variations in different drugs and different patients. Circulation **18**: 348, 1958.

On page 348, paragraph 3 under Method, should read "If D_s is the blood pressure (systolic or diastolic) in the standing posture *during* drug action . . ."

BENTIVOGLIO, L. G., URICCHIO, J. F., WALDOW, A., LIKOFF, W., AND GOLDBERG, H.: An electrocardiographic analysis of sixty-five cases of mitral regurgitation. Circulation **18**: 572, 1958.

On page 575, table 5, Lead V_6, Group Range, 56.0 under LVH should be 36.0; table 5, Lead V_1, No. pts., — (INC) under RVH & IRBBB should be 1.

On page 576, table 6, Lead V_5-V_6, No. pts., 48 (N) and 17 (PRO) under Total should be 49 (N) and 16 (PRO).

On page 577, table 8, R/S Ratio in Lead V_1, No. pts., 37 (N) under Total should be 27.

On page 578, table 9, R Wave in V_1 + S Wave in V_5-V_6, No. pts., 18 (N) under Total should be 19.

FORD, A. B., AND HELLERSTEIN, H. K.: Work and heart disease. I. A physiologic study in the factory. Circulation **18**: 823, 1958.

On page 831, line 13, should read ". . . workers may expend energy at a higher rate *off the job than on it.*"

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

Joint Report of the Research and Social Committees of the International Society of Cardiology, Session in Brussels, September 15 and 19, 1958

The Research Committee and the Social Committee of the International Society of Cardiology met in Joint Sessions on September 15 and 19, 1958, to discuss matters of mutual interest and responsibility. Members of the Committee on Nomenclature and invited experts participated in the meetings. A list of participants is attached to this Report. Members of the Committees continued these discussions between the sessions to obtain agreement. The results are embodied in the following Report to the Council of the Society:

1. Activities and Responsibilities of the Committees

The Research and Social Committees recognize their important responsibilities, especially between the Congresses themselves, in the promotion, on a world-wide basis, of cardiological knowledge and practice and in the campaign against cardiovascular disease. The Committees believe that it is highly desirable to increase their activities in the discharge of those responsibilities with particular emphasis on:

(a) The examination of the needs and the potentialities of international cooperation in cardiovascular research and in the social problems related to diseases of the heart and blood vessels.

(b) The standardization of methods, tests and the reporting of findings in research, especially in surveys, field researches, and other studies on or pertaining to populations and statistical analysis. The Committees believe that in regard to terminology, nomenclature, and classification they have interests in common with the Committee on Nomenclature.

(c) The promotion of the international epidemiological approach to the study of the etiology, natural history, and the possible prevention of cardiovascular disease. This approach should be joined with the approaches by way of laboratory experiments and clinical observations so as to bring all useful scientific disciplines to bear on these problems.

(d) Cooperation with the Committee on Nomenclature, as suggested above, in the development of definitions and classification concerned with cardiovascular disorders and characteristics for the special purposes of research on populations. The Committees ask consideration of the desirability of forming a Tripartite Committee on Research, Social Problems and Nomenclature which, it would be hoped, would continue its deliberation and activity between as well as during the World Congresses.

(e) Assistance in the development of more active cooperation between national and local heart societies, and their respective research and social committees, and all other organizations, especially the International Cardiological Society Research Foundation, that can contribute to the campaign against heart and blood vessel diseases throughout the world. Among the goals of such cooperation are increased provisions for the exchange of research experts as well as of students and fellows, the formation of international research teams and groups and the formulation of cooperative and collaborative projects and programs.

2. Standardization of Methods and Reporting

The increasing use of comparisons between results in different laboratories and in different populations, as a research tool, is applauded by the Committees, but it is noted that

assurance about the validity of such comparisons is essential. The Committees insist on the great importance of standardized methods and the reporting of findings in uniform, clearly defined and objective terms with the least risk of confusion in regard to interpretation. Emphasis should be placed on reporting the actual findings without recourse to interpretation, which would follow later. Accordingly, the Committees note:

(a) An objective classification of electrocardiographic findings has been developed and is being applied in surveys in Greece, Japan, Finland, Italy, Yugoslavia as well as in the United States of America. Without endorsing the details of this system, it is agreed that some such system, after further testing and modification, may be recommended for application in wider research, not to supplant the usual clinical interpretation but simply to provide an agreed framework suitable to statistical analysis without prejudice to any interpretation.

(b) Tentative forms for recording the history, present health, personal habits and the findings in the physical examination, with particular reference to the needs in surveys on cardiovascular disease, have been developed and are now being tested in surveys in the countries mentioned above. One form is intended for screening purposes; a second form provides for recording more detailed information concerning persons suspected of having cardiovascular disease. Both forms provide for the comments and interpretation by the physician but their special feature is the provision for recording fuller details on signs and symptoms in a manner suitable for statistical analysis. The Committees endorse the principles embodied in these forms.

(c) The Committees note the need for similar standardization in objective reporting of the findings in radiological examinations as well as in other tests and measures that may be used in surveys on heart disease. There is particular need for standardization in methods for the measurement of cholesterol and other lipids in the blood. The Committees urge that efforts be made to establish an international center for the control and calibration of blood lipid measurements.

3. Epidemiology of Cardiovascular Disease

The epidemiological approach to the study of the etiology of cardiovascular disease so far has been applied on little more than an exploratory basis but it has already provided valuable information. The need for further development in this area is clear. The Committees urge:

(a) Exploration of possible avenues of financial support for international research on the epidemiology of diseases of the heart and blood vessels. There is a particular need for long-term support of programs aimed at discovering the prevalence, incidence and prognosis of cardiovascular disease in populations differing in the mode of life, including diet, physical activity, personal habits and mental stress, as well as in race and possible genetic constitution. Further, the Committees urge:

(b) The development of strictly comparable survey and follow-up studies in a considerable number of countries and population groups so as to cover the widest possible range of the parameters concerned. It is essential to adopt a common battery of tests and measurements as well as of basic items to be covered in the history and the physical examination. Similar attention should be given to the investigation of the diet, physical activity and social customs. It is important in such comparative investigations to consider the requirements for the eventual separation of the variables by analysis of the combined findings from many separate studies on population groups. The participation of international teams in such programs is recommended to assure identity of methods and criteria as well as to promote international understanding and friendship.

(c) The Committees call attention to current discussions, plans and operations in many countries in regard to the epidemiology of cardiovascular disease. Among the countries concerned, and in which there is strong endorsement of the idea of international cooperation in such research, should be mentioned Italy, Japan, India, Israel, Finland, Norway,

Denmark, Sweden, the Netherlands, Greece, Rumania, Spain, Yugoslavia, South Africa and the United States of America. In many of these and other countries there is need for assistance from experts in various scientific disciplines as well as for financial help. The Committees note with approval the recent steps taken by the World Health Assembly of W.H.O. to aid in the promotion of epidemiological research on incommunicable diseases, including cardiovascular disease. It is hoped that the International Society of Cardiology and the constituent national societies will play an active role in this development.

(d) The Committees believe it is important to recognize the necessity in planning as well as in the operation of such epidemiological studies to provide for the joint efforts, in closely integrated teams, of physicians, biophysicists, biochemists, physiologists, statisticians, social anthropologists, geneticists, and public health administrators.

(e) In the selection of areas and population groups for epidemiological study attention should be paid to the importance of including: (1) areas where it is believed that widely differing frequencies of cardiovascular disease may be found, (2) areas exhibiting great contrasts in the mode of life, especially in the diet, (3) areas where the available statistics suggest discrepancies or special problems, (4) areas where medical standards, facilities, etc., should assure the probability of obtaining the most reliable data.

4. Cardiovascular Fitness

The estimation of cardiovascular fitness is important in the management and rehabilitation of cardiac patients as well as in the evaluation of drugs and methods of management. However, the development, standardization and interpretation of cardiovascular fitness tests at present is inadequate for both research and social needs. While admitting the difficulty of the subject, the Committees recommend:

(a) Stimulation and support of research on methods for the evaluation and enhancement of cardiovascular fitness, with a view both to the needs for exact research and for practical application with a minimum of equipment and specialized personnel.

(b) Formation of study groups and expert panels to give continued attention to the need in this field.

(c) Attention to the concept of positive health in addition to recognition of degree of disability.

5. Other Items

The Committees call attention to the need for more prolonged discussions on all of the items mentioned in this Report. Interim meetings and participation of members in international research should aid in this regard.

Participants in the Joint Committee Meetings at Brussels, Sept. 15 and 19, 1958.

Paul D. White, U.S.A., General Chairman; Gunnar Biörck, Sweden, and Ancel Keys, U.S.A., Vice-Chairmen.

Members of the Nomenclature Committee: Charles Kossmann, U.S.A., and Vittorio Puddu, Italy, Co-Chairmen.

Members of the Research Committee: Ancel Keys, U.S.A., and Paul D. White, U.S.A., Co-Chairmen; Mariano Alimurung, Philippine Islands; John F. Brock, U. of South Africa; P. Duchosal, Switzerland; Noboru Kimura, Japan; J. Lequime, Belgium; Haquin Malmros, Sweden; Vittorio Puddu, Italy; Paul Soisalo, Finland; and E. Wollheim, Germany.

Members of the Social Committee: Gunnar Biörck, Sweden, Chairman; H. K. Hellerstein, U.S.A., and S. Padmavati, India, Vice-Chairmen; William Evans, England; Roger Froment, France; Charles Kossmann, U.S.A.; Blas Moia, Argentina; and F. van Dooren, Belgium.

Invited Participants: E. Cowles Andrus, U.S.A.; Henry Blackburn, U.S.A.; E. Bleger, Norway; Josef Brozek, U.S.A.; Jacques Calotti, France; Francis Chamberlain, U.S.A.; A. Condorelli, Italy; Joseph Doyle, U.S.A.; Frederick H. Epstein, U.S.A.; J. Green, Israel; Tybjaerg Hansen, Denmark; Pentti Hilonen, Finland; Martti Karvonen, Finland; Louis N. Katz, U.S.A.; Felix E. Moore,

U.S.A.; Maurice Nellen, U. of South Africa; D. Papapanayotu, Greece; Arrigo Poppi, Italy; Gibert Quoralto, Spain; Charles H. Rammelkamp, U.S.A.; P. Ryland, Belgium; H. M. Suzman, U. of South Africa; Louis Vogelpoel, U. of South Africa; James Watt, U.S.A.; Robert Wilkins, U.S.A.; and J. Franklin Yeager, U.S.A.

NEW ATTENDANCE RECORD SET AT AHA SCIENTIFIC SESSIONS

A new attendance record of 2352 physicians and scientists was set at the Association's Annual Scientific Sessions in San Francisco. Medical students, nurses, volunteer leaders and staff from Heart Associations raised total attendance at the AHA Annual Meeting to almost 3500. Additional interest in the meeting was fostered by the Scientific Sessions for Clinicians and joint sessions with the American Society for the Study of Arteriosclerosis and the Microcirculatory Conference.

1959 SUBSCRIPTION RENEWALS

Renewals for 1959 subscriptions of *Circulation* and *Circulation Research*, official journals of the American Heart Association, may be made directly through the publisher, Grune and Stratton, Inc., 381 Fourth Avenue, New York 16, N. Y. Subscriptions may be renewed in this manner by members and non-members of the American Heart Association.

EPIDEMIOLOGICAL STUDIES CONFERENCE SCHEDULED

A closed conference to discuss methods of obtaining more uniform data in epidemiological studies of atherosclerosis and hypertension will be sponsored jointly by the American Heart Association and the National Heart Institute on April 24-26, at the Princeton Inn, Princeton, N. J.

INTERIM CHAIRMAN NAMED FOR RESEARCH COMMITTEE

Charles H. Rammelkamp, Jr., M.D. of Cleveland, has been named to serve as interim Chairman of the Association's Research Committee until February, 1959, filling the unexpired term of A. C. Corcoran, M.D., who has resigned. Franklin D. Johnston, M.D., Ann Arbor, Mich., continues as the Committee's Vice Chairman.

INFORMATION BUREAU FOR RHEUMATIC DISEASE STAFFS

To assist in the collection and dissemination of information on professional personnel in the rheumatic disease field, the American Rheumatism Association has established a committee for exchange of information concerning faculty appointees and fellows. Inquiries about fellowship and traineeship opportunities and faculty and other staff vacancies should be addressed to Currier McEwen, M.D., New York University College of Medicine, 550 First Avenue, New York 16, N. Y.

AHA-USPHS STATEMENT URGES FLU VACCINE FOR CARDIACS

A statement recommending that cardiovascular patients obtain vaccinations against influenza has been issued jointly by the American Heart Association and the U.S. Public Health Service, as follows:

"Experience has shown that patients with heart or lung diseases are more susceptible to the hazards of influenza than is the general population. This increased risk is shown by more severe illness and by higher case fatality rates among patients with these diseases. Patients with, or prone to, pulmonary congestion secondary to heart disease are an especially high risk group.

"Studies with influenzal vaccine have clearly shown that its use significantly reduces the incidence and probably the severity of influenzal infection, in the presence of local or widespread epidemics. Furthermore, use of the vaccine is contraindicated only in those patients who are allergic to the components of the vaccine. The type of local and systemic reactions to vaccine have not been such as to constitute any significant hazard to patients with cardiac disease.

"Therefore, the American Heart Association and the Public Health Service, through

its National Heart Institute, wish to call these facts to the attention of all physicians throughout the country. It is further urged that persons with cardiovascular disease consult their physicians as to the advisability of obtaining influenzal vaccination."

MEETINGS CALENDAR

March 17-19: National Health Council, Chicago. Philip E. Ryan, 1790 Broadway, New York 19, N.Y.

April 6-9: American Academy of General Practice, San Francisco. Mac F. Cahal, Volker B'lvd. at Brookside, Kansas City 12, Mo.

April 12-13: American Society for Artificial Internal Organs, Atlantic City. Charles K. Kirby, 110 Maloney Building, Philadelphia, Pa.

April 15-17: American Surgical Association, San Francisco. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 20-24: American College of Physicians, Chicago. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 3: American Federation for Clinical Research, Atlantic City. George E. Schreiner, Georgetown University Hospital, Washington 7, D.C.

May 3-4: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Avenue, New York 16, N.Y.

May 5-6: Association of American Physicians, Atlantic City. Paul B. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 26-29: American College of Cardiology, Philadelphia. Philip Reichert, 480 Park Avenue, New York 22, N.Y.

June 3-7: American College of Chest Physicians, Atlantic City. Murray Kornfeld, 112 E. Chestnut Street, Chicago 11, Ill.

June 8-12: American Medical Association, Atlantic City. F. J. L. Blasingame, 535 N. Dearborn Street, Chicago 10, Ill.

ABROAD

February 19-21: Central Surgical Association, Montreal, Canada. A. D. McLachlin, Victoria Hospital, London, Ontario, Canada.

July 27-30: Shaio Foundation Symposium on Cardiovascular Diseases, Bogota, Colombia. Alberto Vejarano-Laverde, 43-23 Carrera 13, Bogota-Colombia.

CONTRIBUTORS TO THIS ISSUE

PAUL ADAMS, JR., M.D.
ssistant Professor, Department of Pediatrics, niversity of Minnesota, Minneapolis, Minn.

KURT AMPLATZ, M.D.
edical Fellow Specialist, Department of Radiol- y, University of Minnesota, Minneapolis; Trainee Cardiovascular Radiology, National Heart In- tute, U.S. Public Health Service, Bethesda, Md.

JOSEPH T. ANDERSON, PH.D.
Associate Professor of Physiological Hygiene, University of Minnesota School of Public Health, Minneapolis, Minn.

RAY C. ANDERSON, PH.D., M.D.
Assistant Professor, Department of Pediatrics, University of Minnesota, Minneapolis, Minn.

J. HOWLAND AUCHINCLOSS, JR., M.D.
Associate Professor of Medicine, State University of New York, Upstate Medical Center, Syracuse, N.Y. Assistant Attending Physician, Syracuse University and Memorial Hospitals.

FREDERIC C. BARTTER, M.D.
Chief, Section of Endocrinology, Laboratory of General Medicine and Experimental Therapeutics, National Heart Institute, Bethesda, Md.

ROBERT O. BRANDENBURG, M.D., M.S. (MED.)
Consultant, Section of Medicine, Mayo Clinic; Assistant Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

ROBERT CLANCY, M.D.
Assistant Chief of the Medical Service, Veterans Administration Hospital, West Roxbury, Mass.

JAY D. COFFMAN, M.D.
Assistant in Medicine, Boston University School of Medicine; formerly, Resident in Medicine, Massachusetts Memorial Hospitals, Boston, Mass.

BURTON D. COHEN, M.D.
Research Fellow, Cornell University Medical Col- e, 1957-58. Presently, Resident in Medicine, Memorial Center for Cancer and Allied Diseases; Instructor in Medicine, Cornell University Medical College, New York, N.Y.

DANIEL C. CONNOLLY, M.D., M.R.C.P. (IRELAND), PH.D. (MED.)
Consultant, Section of Medicine, Mayo Clinic; Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

JAMES W. DOW, M.D.
Assistant Professor of Medicine, Tufts University School of Medicine; Director of the Circulation Laboratory, Boston City Hospital, Boston, Mass. Presently, Chief of Medicine, The Glover Clinic, and Director of the Circulation Laboratory, The Presbyterian Hospital, Philadelphia, Pa.

ROBERT H. EICH, M.D.
Assistant Professor of Medicine, State University of New York, Upstate Medical Center, Syracuse, N.Y. Assistant Attending Physician, Syracuse University Hospital.

CHARLES K. FRIEDBERG, M.D.
Attending Physician and Cardiologist, The Mount Sinai Hospital; Associate Clinical Professor of Medicine, Columbia University, New York, N.Y.

KORNEL GIBIŃSKI, M.D.
Professor of Internal Medicine; Chief of the Third Clinic of Internal Diseases, Silesian School of Medicine, Bytom, Poland.

ROBERT GILBERT, M.D.
Instructor in Medicine, State University of New York, Upstate Medical Center, Syracuse, N.Y. Veterans Administration Clinical Investigator.

IRA GORE, M.D.
Chief of the Laboratory Service, Veterans Administration Hospital, West Roxbury, Mass.

FRANCISCO GRANDE, M.D.
Professor of Physiological Hygiene, University of Minnesota School of Public Health, Minneapolis, Minn.

NEIL A. J. HAMER, M.B., M.R.C.P.
Assistant Professor of Medicine, Tufts University School of Medicine; Associate Director of the Circulation Laboratory, Boston City Hospital, Boston, Mass. Formerly, Registrar at the National Heart Hospital, London, England.

REVERDY H. JONES, JR., M.D., M.S. (MED.)
On Medical Staff, Lewis-Gale Hospital, Roanoke, Va.

THOMAS J. KENNEDY, JR., M.D.
Senior Investigator, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, Md.

ANCEL KEYS, PH.D.
Professor in the School of Public Health and Director of the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

JOHN W. KIRKLIN, M.D., M.S. (SURG.)
Consultant, Section of Surgery, Mayo Clinic; Associate Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

W. LAURIE, D.S.O., M.D. (GLASG.), T.D.D. (WALES)
Deputy Provincial Pathologist, Natal, South Africa.

RICHARD G. LESTER, M.D.
Assistant Professor, Department of Radiology, University of Minnesota, Minneapolis, Minn.

GLENN D. LUBASH, M.D.
Research Fellow, New York Heart Association, 1957-58; presently, Resident in Medicine Second (Cornell) Medical Divsion, Bellevue Hospital; Instructor in Medicine, Cornell University Medical College, New York, N.Y.

DWIGHT C. MCGOON, M.D.
Consultant, Section of Surgery, Mayo Clinic; Instructor in Surgery, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

LAWRENCE J. MILCH, PH.D.
Chief, Department of Pharmacology and Biochemistry, School of Aviation Medicine, USAF, Randolph Air Force Base, Tex.

JACK ORLOFF, M.D.
Deputy Chief, Laboratory of Kidney and Electrolyte Metabolism, National Heart Institute, Bethesda, Md.

SUJOY B. ROY, M.B., M.R.C.P.
Professor of Cardiology, The All-India Institute of Medical Sciences, New Delhi, India. Formerly, Associate Director of the Circulation Laboratory, Boston City Hospital, and Instructor in Medicine, Tufts University School of Medicine, Boston, Mass. Presently, Associate Director of the Circulation Laboratory, The Presbyterian Hospital, Philadelphia, Pa.

ALBERT L. RUBIN, M.D.
Assistant Professor of Medicine, Cornell University Medical College; Established Investigator, American Heart Association.

GEROLD L. SCHIEBLER, M.D.
Medical Fellow Specialist, Department of Pediatrics, University of Minnesota, Minneapolis, Minn. Trainee on Cardiovascular Disease training grant of the U.S. Public Health Service at the University of Minnesota.

BERNARD S. SCHLESSINGER, PH.D.
Research Chemist, Department of Pharmacology and Biochemistry, School of Aviation Medicine, USAF, Randolph Air Force Base, Tex.

KUNO C. SCHWARZ, M.D.
Assistant Resident, Second (Cornell) Medical Division, Bellevue Hospital; Assistant in Medicine, Cornell University Medical College; presently, Fellow in Medicine, Strong Memorial Hospital, Rochester, N.Y.

JOHN SMITH, M.D.
Resident in Pathology, Veterans Administration Hospital, West Roxbury, Mass.

LOUIS A. SOLOFF, M.D.
Clinical Professor of Medicine; Head of Division of Cardiology, Temple University Medical School and Hospital, Philadelphia, Pa.

SHELDON C. SOMMERS, M.D.
Pathologist, Massachusetts Memorial Hospitals; Associate Professor of Pathology, Boston University School of Medicine, Boston, Mass.

H. J. C. SWAN, M.B., M.R.C.P., PH.D.
Consultant, Section of Physiology, Mayo Clinic; Assistant Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

MACKENZIE WALSER, M.D.
Assistant Professor of Pharmacology and Medicine, Johns Hopkins Medical School, Baltimore, Md.

GERALD H. WHIPPLE, M.D.
Associate in Medicine, Department of Medicine, Boston University Medical School; Physician-in-Charge, Electrocardiography Laboratories, Massachusetts Memorial Hospitals, Boston, Mass.

FREDRICK H. WILSON, JR., B.S.
Research Assistant, Department of Pharmacology and Biochemistry, School of Aviation Medicine, USAF, Randolph Air Force Base, Tex.

J. D. WOODS, M.B. (W'SRAND), F.R.F.P.S., M.R.C.P.
Head of Department of Medicine, Edendale Hospital, Pietermaritzburg, Natal, South Africa.

JACOB ZATUCHNI, M.D.
Associate Professor Medicine, Temple University Medical School and Hospital, Philadelphia, Pa.

why all the fuss over potassium?

Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

Why revive the subject now? Because clinical experience with nonmercurial diuretics indicates most of them have such a specific effect on potassium that with their use very real problems must be faced. Enough potassium loss can lead to digitalis toxicity or to a classical overt hypopotassemia. Since a fair percentage of cardiacs who receive diuretics are also digitalized, this excess potassium excretion is clinically serious. Clinical experience is still too limited with some nonmercurial diuretics to say just how often such loss will occur—but warnings already have been sounded by some clinical investigators as to the need for potassium supplementation.

Experience in many patients, for many years, demonstrates that potassium loss is never a problem when NEOHYDRIN® is the oral diuretic. And there is no refractoriness to this effective oral organomercurial.

LAKESIDE

Circulation

FEBRUARY 1959
VOL. XIX NO. 2

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

EDITORIAL

RHEUMATIC FEVER IN THE ADULT: CRITERIA AND IMPLICATIONS. *Charles K. Friedberg* 161

CLINICAL STUDY OF TWENTY-THREE CASES OF EBSTEIN'S ANOMALY OF THE TRICUSPID VALVE. *Gerold L. Schiebler, Paul Adams, Jr., Ray C. Anderson, Kurt Amplatz and Richard G. Lester* 165

ATRIAL FLUTTER AS A MANIFESTATION OF DIGITALIS TOXICITY. *Jay D. Coffman and Gerald H. Whipple* 188

ATRIAL SEPTAL DEFECT: FACTORS AFFECTING THE SURGICAL MORTALITY RATE. *Dwight C. McGoon, H. J. C. Swan, Robert O. Brandenburg, Daniel C. Connolly and John W. Kirklin* 195

SERUM CHOLESTEROL IN MAN: DIET FAT AND INTRINSIC RESPONSIVENESS. *Ancel Keys, Joseph T. Anderson and Francisco Grande* 201

SEVERE ACIDOSIS AND HYPERPOTASSEMIA TREATED WITH SODIUM BICARBONATE INFUSION. *Kuno C. Schwarz, Burton D. Cohen, Glenn D. Lubash and Albert L. Rubin* 215

CONGENITAL ANEURYSMS OF THE CORONARY ARTERIES WITH REPORT OF A CASE. *Ira Gore, John Smith and Robert Clancy* 221

SPECIAL ARTICLE

BIOCHEMICAL ALTERATIONS IN BLOOD IN OBLITERATIVE ATHEROSCLEROSIS. *Kornel Gibinski* 228

THE PULMONARY DIFFUSING CAPACITY IN CONGENITAL AND RHEUMATIC HEART DISEASE. *J. Howland Auchincloss, Jr., Robert Gilbert and Robert H. Eich* 232

FAMILIAL PSEUDOXANTHOMA ELASTICUM AND VALVULAR HEART DISEASE. *Jay D. Coffman and Sheldon C. Sommers* 242

THE ELECTROCARDIOGRAM OF THE SOUTH AFRICAN BANTU. *J. D. Woods and W. Laurie* 251

DETERMINANTS OF THE LEFT ATRIAL PRESSURE PULSE IN MITRAL VALVE DISEASE. *Neil A. J. Hamer, Sujoy B. Roy and James W. Dow* 257

SERUM PARAMETERS AS DISCRIMINATORS BETWEEN NORMAL AND CORONARY GROUPS. *Bernard S. Schlessinger, Fredrick H. Wilson, Jr., Lawrence J. Milch and the Cardiovascular Research Group* 265

CARDIAC CHAMBER VOLUMES AND THEIR SIGNIFICANCE IN RHEUMATIC HEART DISEASE WITH ISOLATED MITRAL STENOSIS. *Louis A. Soloff and Jacob Zatuchni* 269

CLINICAL PROGRESS

BERIBERI HEART DISEASE. *Reverdy H. Jones, Jr.* 275

CLINICAL CONFERENCE

HYPONATREMIA. *Jack Orloff, MacKenzie Walser, Thomas J. Kennedy, Jr., and Frederic C. Bartter* 284

ABSTRACTS 300

AMERICAN HEART ASSOCIATION 314

CONTRIBUTORS TO THIS ISSUE 319